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Synthesis of Furan Derivatives. LXXXVIII.[1] Reactivity of Tosylmethyl Isocyanide towards Azole Carbaldehydes

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Tosylmethyl isocyanide (**4**) reacted readily with azole carbaldehydes, *i.e.*, indole-2-carbaldehyde (**8a**), pyrazole-3(5)-carbaldehyde (**8b**), 3(5)-methylpyrazole-5(3)-carbaldehyde (**8c**), 3(5)-(2-furyl)pyrazole-5(3)-carbaldehyde(**8d**), 1,2,4-triazole-3(5)-carbaldehyde(**8e**), and tetrazole-5-carbaldehyde (**8f**), in the presence of an equimolar amount of potassium carbonate in refluxing methanol to yield the corresponding 5-substituted oxazoles (**10** and **15b**—**f**) as the final products.

In the case of the reaction of **4** with imidazole-2-carbaldehyde (**8g**), however, *N*-(1-tosyl-1-alkenyl)formamide of type **18g**, 1-amino-1-tosyl-2-alkene of type **19g**, and 3-tosylimidazo[1,2-*c*]pyrimidine (**22g**) were obtained, depending on the reaction conditions.

Keywords——azole carbaldehyde; tosylmethyl isocyanide; cycloaddition reaction; 5-substituted oxazole; dehydration; alkenylamine; alkenylformamide; imidazo[1,2-*c*]-pyrimidine

It has been demonstrated[2] that the base-catalyzed cyclization of methyl isocyanoacetate (**1**) with pyrrole-2-carbaldehydes (**2**) proceeds to give 3-methoxycarbonylpyrrolo[1,2-*c*]pyrimidines (**3**). Independently, in the course of our studies on the reaction of tosylmethyl isocyanide (TosMIC) (**4**)[3] with heteroaromatic carbaldehydes with the aim of preparing the

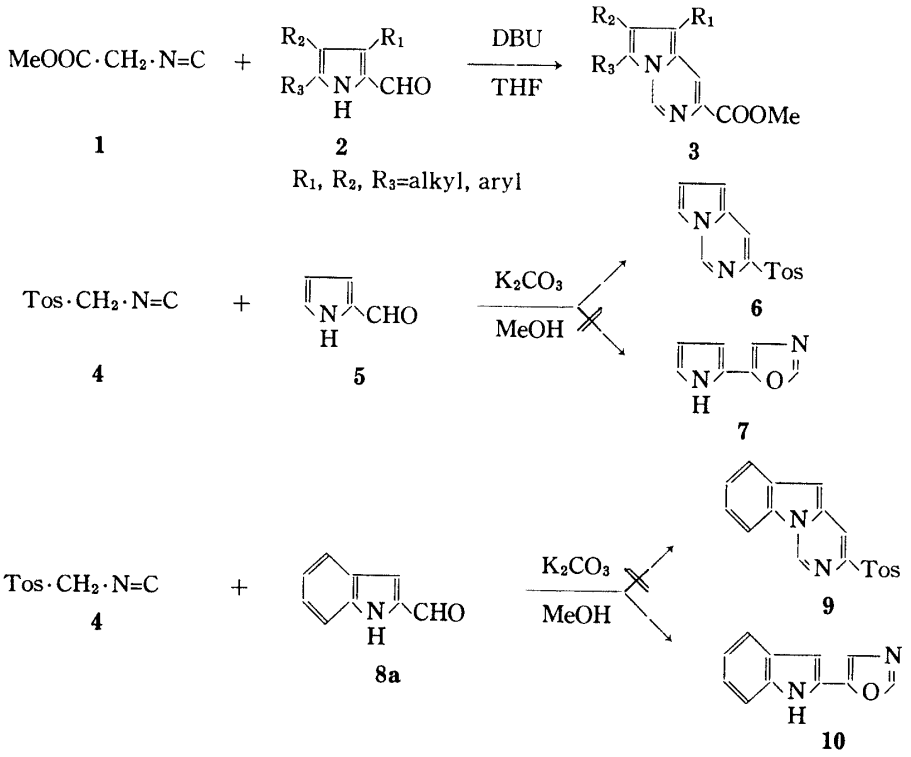
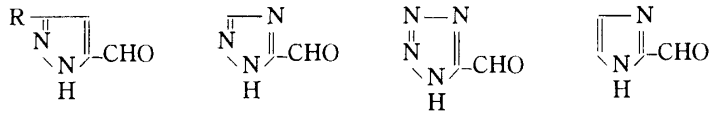


Chart 1

corresponding oxazoles, we reported[4] that the treatment of TosMIC (**4**) with pyrrole-2-carbaldehyde (**5**) using potassium carbonate (K_2CO_3) as a base in refluxing methanol led unexpectedly to the formation of 3-tosylpyrrolo [1, 2-*c*]pyrimidine (**6**) in 20% yield rather than to that of the corresponding 5-substituted oxazole (**7**). Interestingly, we have found that indole-2-carbaldehyde (**8a**) reacts readily with TosMIC (**4**) under the preceding reaction conditions to give, not the corresponding pyrimidine derivative (**9**), but 5-(2-indolyl)oxazole (**10**) in 86% yield as shown in Chart 1.

In connection with these findings, we report herein the results of the reaction of TosMIC (**4**) with azole carbaldehydes (**8b**—**g**) as shown in Chart 2.



8b—d **8e** **8f** **8g**

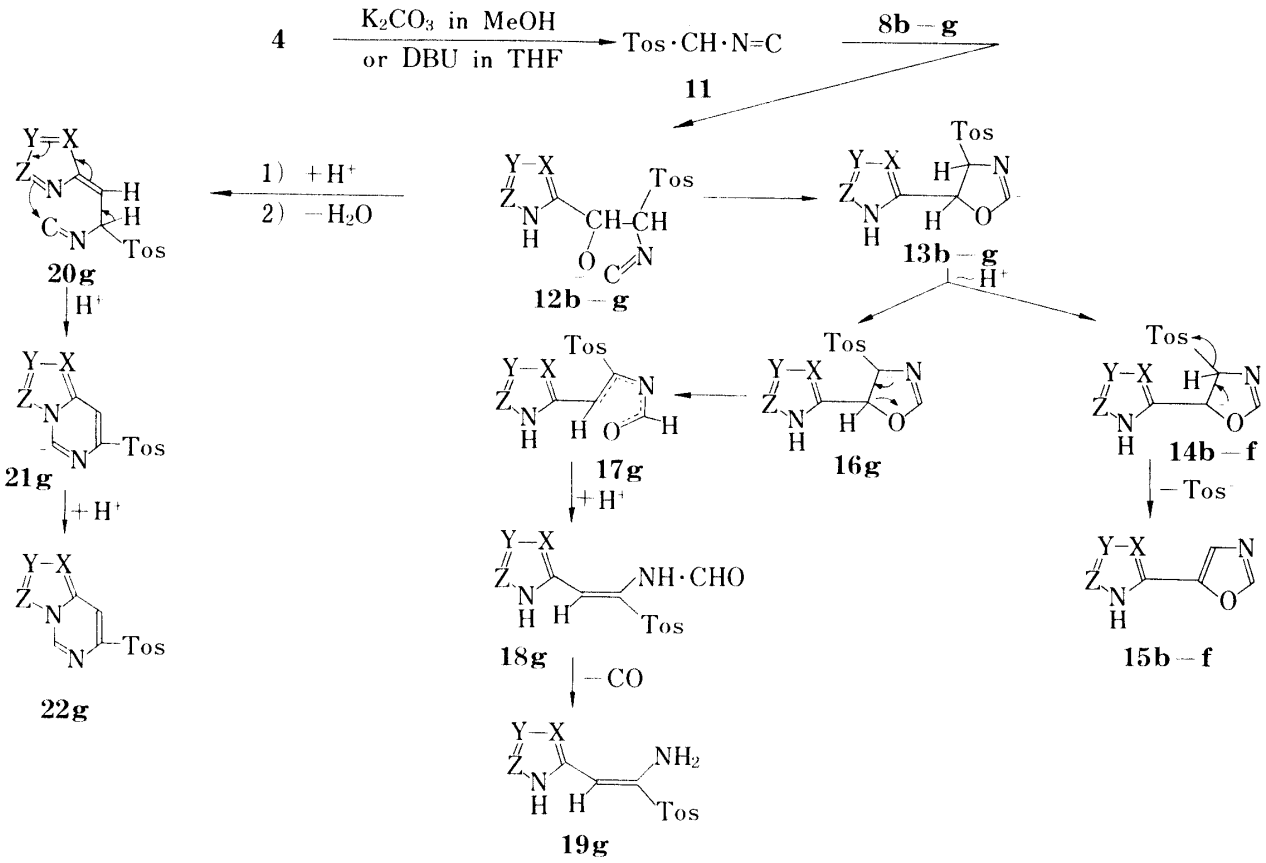
8b: R=H
8c: R=CH_3
8d: R=

Chart 2

When the reaction was carried out in the presence of an equimolar amount of K_2CO_3 in refluxing methanol for 2 h, pyrazole-3(5)-carbaldehyde (**8b**), 3(5)-methylpyrazole-5(3)-carbaldehyde (**8c**), 3(5)-(2-furyl)pyrazole-5(3)-carbaldehyde (**8d**), 1,2,4-triazole-3(5)-carbaldehyde (**8e**), and tetrazole-5-carbaldehyde (**8f**) reacted with **4** to give the corresponding 5-substituted oxazoles (**15b**—**f**) as shown in Chart 3. Under the same conditions, the reaction of TosMIC (**4**) with imidazole-2-carbaldehyde (**8g**), however, did not afford the corresponding oxazole such as **15**. Instead, only 1-amino-1-tosyl-2-(2-imidazolyl)ethylene (**19g**)[5] was obtained in 79% yield. In the reaction at lower temperature (5°C), the intermediate *N*-[2-(2-inidazolyl)-1-tosylvinyl]formamide (**18g**; 26%) was isolated along with **19g** (4%), and it was confirmed that the deformylation of **18g** proceeded smoothly under reflux for 2 h with K_2CO_3 in methanol to give a 78% yield of **19g**.

On the other hand, the reaction of **4** with imidazole-2-carbaldehyde (**8g**) for 1 h at room temperature, using 1,8-diazabicylo[5. 4. 0]undec-7-ene (DBU) as a base in tetrahydrofuran (THF) in place of K_2CO_3 in methanol, resulted in a 14% yield of 3-tosylimidazo[1, 2-*c*]pyrimidine (**22g**) together with a large amount of tarry product. While the analogous formation of pyrrolo[1, 2-*c*]pyrimidines (**6**) from the reaction of **4** with pyrrole-2-carbaldehyde (**5**) has been described,[4] we suggest again here that the formation of **22g** probably involves the cyclization of an intermediate (**20g**), following the elimination of water from a primary adduct (**12g**). If this is so, this dehydration, which takes precedence over the ring closure from **12g** to an oxazoline (**13g**), seems to be an essential prerequisite to form a pyrimidine ring (**21g**). All attempts to prepare pyrimidines of type **22** from the reaction of **4** with the azole carbaldehydes (**8a**—**f**) using DBU in THF unfortunately failed; each of the reaction mixtures turned dark-brown as soon as the DBU solution was dropped in, and then deposited tarry products, even though the reactions were carried out at a temperature below 0°C. The failure to obtain the desired pyrimidines of type **22** may be attributable to the basicity of DBU being too high, resulting in the decomposition of the azole carbaldehydes (**8a**—**f**) and/or their derivatives.

In view of the reaction of TosMIC (**4**) with the series of the simple azole carbaldehydes (**8a**—**g**), imino hydrogens in the azole rings are not always involved in the dehydration of the primary adduct of type **12**. Actually, in the case of the reaction of **4** with imidazole-2-carbaldehyde (**8g**), it may be presumed that the predominant route of reaction of the primary adduct



12, 13, and 16—22	X	Y	Z
g	N	CH	CH

12—15	X	Y	Z
b	CH	CH	N
c	CH	C-CH_3	N
d	CH	C-(2-furyl)	N
e	N	CH	N
f	N	N	N

Chart 3

(**12g**) depends entirely upon the reaction condition, such as the nature of the base (K_2CO_3 or DBU), and the mobility of the imino hydrogen in the imidazole ring.

In conclusion, the final products in the reaction of TosMIC (**4**) with the azole carbaldehydes (**8a—f**) other than inidazole-2-carbaldehyde (**8g**), using K_2CO_3 in refluxing methanol, were the corresponding oxazoles (**10** and **15b—f**). From the reaction of TosMIC (**4**) with **8g**, however, *N*-[2-(imidazolyl)-1-tosylvinyl]formamide (**18g**), 1-amino-1-tosyl-2-(2-imidazolyl)ethylene(**19g**), or 3-tosylimidazo[1, 2-*c*]pyrimidine (**22g**) were obtained, depending on the conditions of the reaction.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured on a Hitachi 215 infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL model C-100 NMR spectrometer at 100 MHz, with tetramethylsilane as an internal reference. Mass spectra were measured on a Hitachi mass spectrometer, model RMU-6MG.

Indole-2-carbaldehyde (**8a**),[6] pyrazole-3(5)-carbaldehyde (**8b**),[7] 3(5)-methylpyrazole-5(3)-carbaldehyde (**8c**),[7] 1,2,4-triazole-3(5)-carbaldehyde (**8e**),[8] and imidazole-2-carbaldehyde (**8g**)[9] were prepared by the cited procedures.

3(5)-Hydroxymethyl-5(3)-(2-furyl)pyrazole——A dry ether solution (100 ml) of ethyl 3(5)-(2-furyl)-pyrazole-5(3)-carboxylate[10] (8.2 g, 40 mmol) was added dropwise to a dry ether suspension (250 ml) of lithium aluminum hydride (2 g, 48 mmol) at a rate sufficient to keep the solution boiling, with stirring. When the addition was complete, stirring was continued for fifteen minutes, and 100 ml of water was added slowly to decompose the excess reducing agent. The ether layer was separated, washed with water and dried over magnesium sulfate. The ether was evaporated off and the residue was recrystallized from benzene to give 5.7 g (86%) of the title compound as colorless needles, mp 87—88°C. *Anal.* Calcd for $C_8H_8N_2O_2$ C, 58.53; H, 4.91; N, 17.07. Found: C, 58.41; H, 4.85; N, 17.01.

3(5)-(2-Furyl)pyrazole-5(3)-carbaldehyde (**8d**)——Activated manganese dioxide[11] (50 g) was added portionwise to an acetone solution (800 ml) of 3(5)-hydroxymethyl-5(3)-(2-furyl)pyrazole (6.6 g, 40 mmol) (see the above experiment) at 10°C for a period of 15 min with stirring. The resulting mixture was stirred for 48 h at room temperature and filtered, then the clear filtrate was concentrated *in vacuo* to provide 6.7 g of crude product, which was recrystallized from benzene/cyclohexane (1/4) yielding 6.1 g (94%) of **8d**; yellow prisms, mp 178—180°C. *Anal.* Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.48; H, 3.83; N, 17.19.

Tetrazole-5-carbaldehyde (**8f**)——According to the method described above for the preparation of **8d**, 5-hydroxymethyltetrazole[12] (3 g, 30 mmol) was oxidized with activated manganese dioxide[11] (**18g**) in acetone (300 ml) for 7 d at room temperature, and the resulting suspension was worked up as described for **8d** to give 2.8 g of **8f** as an oil, which was used as such for the next reaction with TosMIC (**4**).

5-(2-Indolyl)oxazole (**10**)——Anhydrous K_2CO_3 (0.93 g, 6.8 mmol) was added to a methanol solution (30 ml) of indole-2-carbaldehyde (**8a**)[6] (1 g, 6.8 mmol) and TosMIC (**4**) (1.34 g, 6.8 mmol) with stirring. The resulting mixture was gently refluxed on a water-bath for 2 h, and then the solvent was evaporated off *in vacuo*. The resulting residue was poured into ice-water, and extracted with ethyl acetate. The extract was washed with 2% hydrochloric acid and water, then dried over anhydrous sodium sulfate. The organic solvent was evaporated off *in vacuo*, and the crystalline mass obtained was recrystallized from benzene/cyclohexane (1/4) to give 0.93 g (74%) of **10**; colorless needles, mp 157—158°C. *Anal.* Calcd for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 72.05; H, 4.33; N, 15.20. UV λ_{max}^{EtOH} nm (log ε): 307 (4.39). IR ν_{max}^{KBr} cm^{-1}: 3100 (C–H), 1640 (C=N), 1610 (C=C). NMR ($CDCl_3$) δ: 6.82 (s, 1H, 3′-H), 7.28 (s, 1H, 4-H), 7.90 (s, 1H, 2-H), 8.56 (br s, 1H, N–H), 7.00—7.77 (m, 4H, benzene-H). MS *m/e*: 184 (M^+).

5-[3(5)-Pyrazolyl]oxazole (**15b**)——According to the method described above for the preparation of **10**, the reaction of pyrazole-3(5)-carbaldehyde (**8b**)[7] (1.44 g, 15 mmol), TosMIC (**4**) (2.9 g, 15 mmol), and anhydrous K_2CO_3 (2 g, 15 mmol) in 40 ml of methanol afforded 0.9 g (44%) of **15b**; colorless needles from benzene, mp 130—132°C. *Anal.* Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.44; H, 3.60; N, 31.02. IR ν_{max}^{KBr} cm^{-1}: 3090 (C–H), 1620 (C=C or C=N). UV λ_{max}^{EtOH} nm (log ε): 248 (4.18). NMR ($CDCl_3$) δ: 6.62 (s, 1H, 4′-H), 7.46 (s, 1H, 4-H), 7.84 (s, 1H, 3′-H), 8.40 (s, 1H, 2-H), 13.16 (br s, 1H, N–H). MS *m/e*: 135 (M^+).

5-[3(5)-Methyl-5(3)-pyrazolyl]oxazole (**15c**)——According to the method described above for the preparation of **10**, the reaction of 3(5)-methylpyrazole-5(3)-carbaldehyde (**8c**)[7] (1.1 g, 10 mmol), **4** (2.0 g, 10 mmol) and anhydrous K_2CO_3 (1.3 g, 10 mmol) in 30 ml of methanol afforded 0.7 g (46%) of **15c**; colorless plates from benzene, mp 118—120°C. *Anal.* Calcd for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.39; H, 4.65; N, 28.13. IR ν_{max}^{KBr} cm^{-1}: 3100 (C–H), 1640 (C=N), 1600 (C=C). UV λ_{max}^{EtOH} nm (log ε): 251 (4.14). NMR ($CDCl_3$) δ: 2.36 (s, 3H, $-CH_3$), 6.30 (s, 1H, 4′-H), 7.24 (s, 1H, 4-H), 7.86 (s, 1H, 2-H). MS *m/e*: 149 (M^+).

5-[3(5)-(2-Furyl)-5(3)-pyrazolyl]oxazole (**15d**)——According to the method described above for the preparation of **10**, the reaction of 3(5)-(2-furyl)pyrazole-5(3)-carbaldehyde (**8d**) (1.4 g, 8.6 mmol), **4** (1.7 g, 8.6 mmol) and anhydrous K_2CO_3 (1.2 g, 8.6 mmol) in 50 ml of methanol afforded 0.3 g (17%) of **15d**; pale yellow plates from benzene, mp 155—157°C. *Anal.* Calcd for $C_{10}H_7N_3O_2$; C, 59.70; H, 3.51; N, 20.89. Found: C, 59.85; H, 3.43; N, 20.75. IR ν_{max}^{KBr} cm^{-1}: 3100 (C–H), 1630 (C=N). UV λ_{max}^{EtOH} nm (log ε): 262 (4.46). NMR ($CDCl_3$) δ: 6.5 (dd, $J_{4,3}=4$ Hz, $J_{4,5}=2$ Hz, 1H, furan, 4-H), 6.66 (d, $J_{3,4}=4$ Hz, 1H, furan, 3-H), 6.72 (s, 1H, pyrazole, 4-H), 7.4 (s, 1H, oxazole, 4-H), 7.46 (d, $J_{5,4}=2$ Hz, 1H, furan, 5-H), 7.9 (s, 1H, oxazole, 2H). MS *m/e*: 201 (M^+).

3(5)-(5-Oxazolyl)-1,2,4-triazole (**15e**)——According to the method described above for the preparation of **10**, the reaction of 1,2,4-triazole-3(5)-carbaldehyde (**8e**)[8] (0.49 g, 5 mmol), **4** (0.98 g, 5 mmol) and anhydrous K_2CO_3 (0.7 g, 5 mmol) in 30 ml of methanol afforded 0.6 g (87%) of **15e**; colorless prisms from benzene, mp 226—228°C. *Anal.* Calcd for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.20; H, 2.88; N, 41.13. IR ν_{max}^{KBr} cm^{-1}: 3100 (C–H), 1640 (C=N). UV λ_{max}^{EtOH} nm (log ε): 246 (4.10). NMR ($CDCl_3$) δ: 7.68 (s, 1H, 4-H), 8.54 (s, 1H, 2-H), 8.66 (s, 1H, 3′-H), 14.44 (br s, 1H, N–H). MS *m/e*: 136 (M^+).

5-(5-Oxazolyl)tetrazole (**15f**)——According to the method described above for the preparation of **10**, the reaction of tetrazole-5-carbaldehyde (**8f**) (1 g, 10 mmol), **4** (2 g, 10 mmol) and anhydrous K_2CO_3 (1.4 g, 10 mmol) in 50 ml of methanol afforded 1.2 g (87%) of **15f**; colorless needles from ethyl acetate, mp 204—206°C. *Anal.* Calcd for $C_4H_3N_5O$: C, 35.04; H, 2.21; N, 51.09. Found: C, 34.87; H, 2.11; N, 51.25. IR ν_{max}^{KBr}

cm^{-1}: 3400 (br N–H), 1640 (C=N). UV λ_{max}^{EtOH} nm (log ε): 243 (4.09). NMR (DMSO-d_6) δ: 7.96 (s, 1H, 4-H), 8.74 (s, 1H, 2-H). MS *m/e*: 137 (M^+).

1-Amino-1-tosyl-2-(2-imidazolyl)ethylene (19g)——Method A: Anhydrous K_2CO_3 (1.3 g, 10 mmol) was added to a methanol solution (30 ml) of imidazole-2-carbaldehyde (**8g**)[9] (0.96 g, 10 mmol) and **4** (1.95 g, 10 mmol) with stirring. The resulting mixture was gently refluxed on a water-bath for 2 h, and then the solvent was evaporated off *in vacuo*. The resulting residue was poured into ice-water, and extracted with ethyl acetate. The extract was washed with water, and then dried over anhydrous sodium sulfate. The organic solvent was evaporated off, and the residue was recrystallized from benzene to give 2.1 g (79%) of **19g**; colorless needles, mp 119—121°C. *Anal.* Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.98; H, 4.91; N, 15.73. IR ν_{max}^{KBr} cm^{-1}: 3350 (N–H), 1630 (C=C), 1320 and 1140 (SO_2). UV λ_{max}^{EtOH}nm (log ε): 227 (4.21) and 285 (4.08). NMR (DMSO-d_6) δ: 2.32 (s, 3H, $-CH_3$), 6.92 (m, 2H, imidazole, 4- and 5-H), 7.3—7.9 (m, 5H, phenyl- and vinyl-H), 9.0 (br s, 2H, $-NH_2$), 11.1 (br s, 1H, N–H). MS *m/e*: 263 (M^+).

Method B: The reaction mixture of **18g** (see below) (100 mg, 0.34 mmol) and anhydrous K_2CO_3 (47 mg, 0.24 mmol) in 5 ml of methanol was gently refluxed for 2 h to give 70 mg (78%) of **19g**. A mixed melting point determination of this compound and the product obtained by method A showed no depression. The IR spectra of the two samples were identical.

***N*-[2-(2-Imidazolyl)-1-tosylvinyl]formamide (18g)**——Anhydrous K_2CO_3 (1.38 g, 10 mmol) was added to a methanol solution (100 ml) of **8g** (0.96 g, 10 mmol) and **4** (1.95 g, 10 mmol) at 5°C with stirring. The resulting mixture was stirred for 2 h at room temperature, then the methanol was evaporated off *in vacuo*. The resulting residue was poured into water, and extracted with ethyl acetate. The water phase containing **18g** was concentrated *in vacuo* to give a crystalline mass, which was developed on a silica gel column with benzene/ethanol (19/1 v/v). Concentration of the first eluate (30 ml) gave 0.7 g (26%) of **18g**; colorless prisms from benzene, mp 201—203°C. *Anal.* Calcd for $C_{13}H_{13}N_3O_3S$: C, 53.61; H, 4.51; N, 14.43. Found: C, 53.54; H, 4.46; N, 14.38. IR ν_{max}^{KBr} cm^{-1}: 3350 (N–H), 1710 (C=O), 1620 (C=C), 1320 and 1130 (SO_2). UV λ_{max}^{EtOH} nm (log ε): 222 (4.17), 244 (4.24), 309 (4.16). NMR (DMSO-d_6) δ: 2.32 (s, 3H, $-CH_3$), 7.12 (s, 2H, imidazole 4- and 5-H), 7.36 (d, 2H, J=8 Hz, phenyl 3- and 5-H), 7.86 (d, 2H, J=8 Hz, phenyl 2- and 6-H), 8.20 (s, 1H, vinyl-H), 8.68 (s, 1H, –CHO), 11.8 (br s, 2H, N–H). MS *m/e*: 291 (M^+).

The ethyl acetate phase containing **19g** was washed with water, and dried over anhydrous sodium sulfate. The organic solvent was concentrated *in vacuo*, and the resulting residue was recrystallized from benzene to give 120 mg (4%) of **19g**.

3-Tosylimidazo[1,2-*c*]pyrimidine (22g)——A THF solution (20 ml) of DBU (1.52 g, 10 mmol) was added dropwise to a THF solution (30 ml) of **8g** (0.96 g, 10 mmol) and **4** (1.95 g, 10 mmol) at 5°C during a period of 10 min with stirring. Stirring was continued at 50°C for 10 min, then glacial acetic acid (0.6 g, 10 mmol) was added, and the solvent was evaporated off *in vacuo*. The resulting residue was poured into water, and extracted with ethyl acetate. The extract was washed with water, and dried over anhydrous sodium sulfate, then the organic solvent was evaporated off *in vacuo*. the crystalline mass obtained was recrystallized from ethanol to give 400 mg (14%) of **22g**; colorless prisms, mp 225—227°C. *Anal.* Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.30; H, 3.83; N, 15.41. IR ν_{max}^{KBr} cm^{-1}: 1600 (C=C), 1320 and 1140 (SO_2). UV λ_{max}^{EtOH} nm (log ε): 237 (4.21), 276 (3.94), and 314 (3.87). NMR (DMSO-d_6) δ: 2.40 (s, 3H, $-CH_3$), 7.46 (d, 2H, J=8 Hz, phenyl 3- and 5-H), 7.92 (d, 2H, phenyl 2- and 6-H), 7.9 (d, 1H, J=2 Hz, 8-H), 8.24 (s, 1H, 2-H), 8.4 (s, 1H, 3-H), 9.5 (d, 1H, J=2 Hz, 5-H). MS *m/e*: 273 (M^+).

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References and Notes

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