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Thermal Rearrangements of Cyclic Amine Ylides. III.[1] Intramolecular Cyclization of 2-Ethynylpyridine *N*-Imides to 3-Azaindolizine Derivatives

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Treatment of the *N*-aminopyridinium salts (**5a**—**e**) prepared from 2-ethynylpyridines (**4**) with potassium carbonate resulted in an intramolecular cyclization to give the corresponding 3-azaindolizines (**6**) (pyrazolo[2,3-*a*]pyridines), presumably *via* the ionic intermediates (**8**) and (**9**). Similarly, pyrazolo[2,3-*a*]quinolines (**13a**—**c**), pyrazolo[3,2-*a*]isoquinolines (**16a**—**c**), and pyrazolo[2,3-*b*]isoquinolines (**19a**—**c**) were obtained from the corresponding ethynylquinolines (**11**) or ethynylisoquinolines (**14**, **17**) *via* the *N*-amino salts (**12**, **15**, or **18**).

Keywords——intramolecular cyclization; rearrangement; *N*-imide; 2-ethynylpyridine; 2-ethynylquinoline; ethynylisoquinoline; 3-azaindolizine; pyrazolo[2,3-*a*]quinoline; pyrazolo-[3,2-*a*]isoquinoline; pyrazolo[2,3-*b*]isoquinoline

The chemistry of amine *N*-imides,[1-4] as well as that of sulfur ylides[5] and amine *N*-oxides,[6] has recently been an area of intense investigation. One reason for this interest is that *N*-imides can be used as reactive intermediates in organic synthesis, particularly in the synthesis of *N*-hetereocycles. Aromatic amine *N*-imides are known to undergo photochemical rearrangements to give various types of diazaheterocyclic ring systems such as 1,2-diazepines and 1,3-diazepines.[7] The intermolecular 1,3-dipolar cycloaddition of pyridine *N*-imides (**1**) and related compounds to olefins or acetylenes and the intramolecular 1,5-dipolar cycloaddition of the vinylazomethine imides (**2**) have also been widely studied.[3] However, few such reactions of pyridine *N*-imides with an unsaturated substituent in the α-position of the pyridine ring are known.

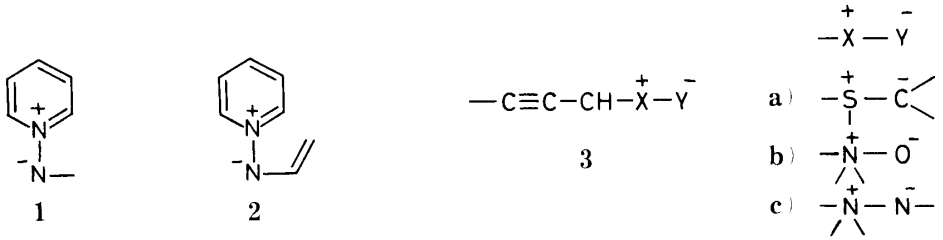


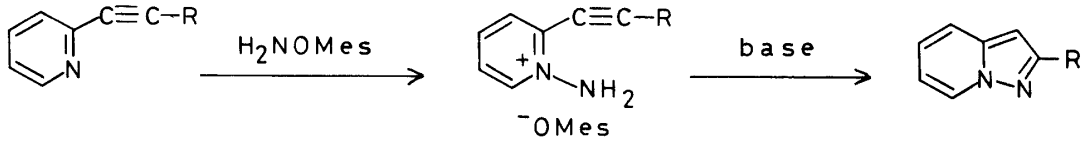
Chart 1

On the other hand, propargylic *S*-ylides (**3a**),[8] *N*-oxides (**3b**),[9] and *N*-imides (**3c**)[10] are known to undergo thermal [2,3]-sigmatropic rearrangement to give allenic compounds. Therefore, we were interested in examining the thermal behavior of 2-ethynylpyridine *N*-imides and related benzo analogs, and now report the formation of the corresponding 3-azaindolizine derivatives.[11]

The required 2-ethynylpyridines (**4a**—**e**) were prepared from 2-vinylpyridine or 2-bromopyridine according to the method of Leaver *et al.*[12] or Sonogashira *et al.*[13] The

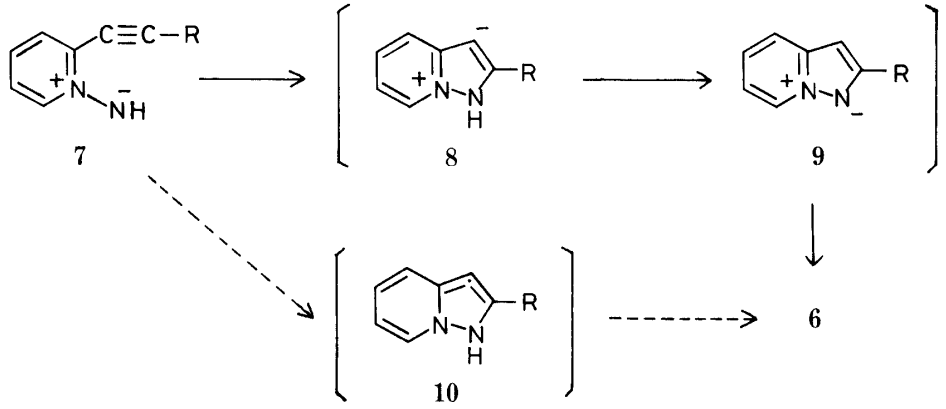
ethynylpyridines (**4**) were aminated with *O*-mesitylenesulfonylhydroxylamine (H_2NOMes)[14] in methylene chloride to give the *N*-aminopyridinium mesitylenesulfonates (**5**) in 75—90% yields. The salts (**5**) thus obtained were treated with potassium carbonate in dimethylformamide at room temperature to give the corresponding 3-azaindolizines (**6**), pyrazolo[2,3-*a*]pyridines. The yields of **6** depend on both the solvents and bases used. Dimethylformamide gave higher yields than did water or alcohols, and carbonates were better than hydroxides or bicarbonates for this reaction.

Unsubstituted- (**6a**) and 2-phenyl-3-azaindolizine (**6e**) were identical with authentic samples prepared from 2-(β-aminoethyl)pyridine by the method of Bower *et al.*[15] The other products (**6b—d**) were characterized by spectral comparison with **6a**, **e**.



4 5 6

a : R=H; **b** : R=Me; **c** : R=*n*-Bu; **d** : R=CH_2OH; **e** : R=Ph



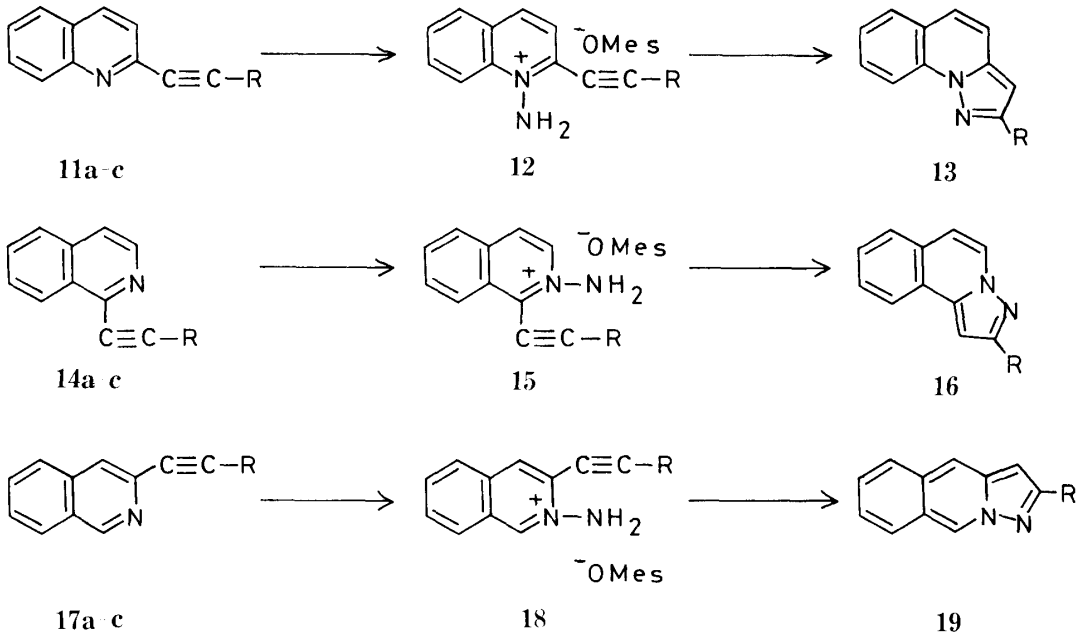
7 8 9 10 6

Chart 2

A possible mechanism for the reaction is shown in Chart 2. The *N*-imides (**7**) initially formed from the salts (**5**) by base treatment may cyclize to give the zwitter-ionic intermediates (**8**). The intermediates (**8**) may then undergo a 1,3-hydrogen shift to the imide intermediates (**9**), which give the products (**6**). As stated above, the aliphatic amine *N*-oxides (**3b**) and *N*-imides (**3c**) give allene compounds by thermal [2,3]-sigmatropic rearrangement. However, a concerted mechanism *via* the intermediates (**10**) for the present reaction seems unlikely because of prohibitive ring strain in the five-membered cyclic allene intermediates.

Similarly, the *N*-aminoquinolinium salts (**12a—c**), prepared from the 2-ethynylquinolines (**11**) by the reported method,[16] upon treatment with potassium carbonate in dimethylformamide gave the corresponding pyrazolo[2,3-*a*]quinolines (**13**). The pyrazolo[3,2-*a*]isoquinolines (**16a—c**) and pyrazolo[2,3-*b*]isoquinolines (**19a—c**) were also obtained from the 1-ethynylisoquinolines (**14**)[16] or 3-ethynylisoquinolines (**17**)[16] *via* the corresponding *N*-amino salts (**15**) or (**18**).

3-Azaindolizines with an electron-withdrawing substituent such as an acyl, cyano, or nitro group in the 1- and/or 2-position can be prepared from the pyridine *N*-imides (**1**) or (**2**) by 1,3-dipolar cycloaddition to acetylenes or by 1,5-dipolar cyclization, but unsubstituted and



a : R = *n*-Bu; b : R = CH_2OH; c : R = Ph

Chart 3

alkyl-substituted 3-azaindolizines are little known. The present results provide a useful new method for preparing simple 3-azaindolizines and their benzo derivatives, which have not been obtained by the 1,3-dipolar cycloaddition of pyridine *N*-imides.

Experimental

Melting points were measured on a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were determined with a JASCO IRA-2 spectrometer and mass spectra (MS) were recorded on a JEOL D-100 instrument. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-MH100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard; spectral assignments were confirmed by spin-decoupling experiments. Microanalyses were performed in the Microanalytical Laboratory of this school by Mrs. R. Igarashi.

2-Ethynylpyridines (4a—e)——2-Ethynylpyridines (**4a**) was prepared from 2-vinylpyridine by the method of Leaver *et al.*[12] 2-Hydoxylmethylethynyl- (**4d**) and 2-phenylethynylpyridine (**4e**) were prepared from 2-bromopyridine by the method of Sonogashira *et al.*[13] The new compounds, 2-methylethynyl- (**4b**) and 2-*n*-butylethynyl-pyridine (**4c**), were prepared from 2-bromopyridine according to the procedures used for **4d, e**. Spectral data for the known compounds (**4a, d, e**) were not given in the literature, so they are also reported here.

4a: Colorless oil, bp 90 °C (30 mmHg) [lit.[12] bp 86—88 °C (14 mmHg)]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250. MS *m/e*: 103 (M^+). NMR δ: 3.40 (1H, s, C≡CH), 7.1—7.8 (3H, m, 3-, 4-, and 5-H), 8.54 (1H, d, J=5 Hz, 6-H).

4b: Pale yellow oil, bp 97—101 °C (15 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2230. MS *m/e*: 117 (M^+). NMR δ: 2.04 (3H, s, Me), 7.20 (1H, dd, 5-H), 7.39 (1H, d, 3-H), 7.64 (1H, dd, 4-H), 8.58 (1H, d, 6-H), $J_{3,4}$=8, $J_{4,5}$=8, $J_{5,6}$=5 Hz. *Anal.* Calcd for C_8H_7N: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.83; H, 6.04; N, 11.91.

4c: Pale yellow oil, bp 115 °C (6 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250. MS *m/e*: 159 (M^+). NMR δ: *n*-Bu [0.90 (3H, t, J=7 Hz), 1.3—1.7 (4H, m), and 2.4 (2H, m)], 7.10 (1H, dd, 5-H), 7.30 (1H, d, 3-H), 7.54 (1H, dd, 4-H), 8.48 (1H, d, 6-H), $J_{3,4}$=8, $J_{4,5}$=7, $J_{5,6}$=5 Hz. *Anal.* Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 83.08; H, 8.25; N, 8.66.

4d: Pale yellow prisms, mp 81—83 °C, bp 120—123 °C (3 mmHg) [lit.[13] bp 124 °C (3 mmHg)]. IR ν_{max}^{KBr} cm^{-1}: 3200, 2250. MS *m/e*: 121 (M^+). NMR δ: 4.54 (2H, s, CH_2OH), 5.8 (1H, br, OH), 7.0—7.6 (3H, m, 3-, 4-, and 5-H), 8.5 (1H, d, J=5 Hz, 6-H).

4e: Pale yellow oil, bp 180—182 °C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2230. MS *m/e*: 179 (M^+). NMR δ: 7.0—7.6 (8H, m), 8.52 (1H, d, J=5 Hz, 6-H).

***N*-Amino-2-ethynylpyridinium Mesitylenesulfonates (5a—e)**——General Procedure: A solution of *O*-mesitylenesulfonylhydroxylamine (1.1 mol eq) in CH_2Cl_2 (20—30 ml) was added dropwise to a solution of an

ethynylpyridine (**4**: 0.02—0.03 mol) in CH_2Cl_2 (10—20 ml) with constant stirring in an ice bath. The reaction mixture was stirred for an additional 30 min and the ether (300—500 ml) was added to the mixture. The resulting crystalline precipitate was collected by filtration and recrystallized from MeOH–AcOEt to give the corresponding salt (**5**).

5a: 75% yield, mp 115—116 °C, colorless needles. *Anal.* Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.38; H, 5.66; N, 8.80. Found: C, 60.18; H, 5.67; N, 8.82.

5b: 91% yield, mp 123—125 °C, colorless needles. *Anal.* Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.45; H, 6.02; N, 8.43. Found: C, 61.76; H, 6.25; N, 8.40.

5c: 90% yield, mp 99—100.5 °C, colorless prisms. *Anal.* Calcd for $C_{20}H_{26}N_2O_3S$: C, 64.17; H, 6.95; N, 7.48. Found: C, 63.92; H, 6.97; N, 7.16.

5d: 84% yield, mp 104—106 °C, colorless prisms. *Anal.* Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.62; H, 5.75; N, 8.06. Found: C, 58.50; H, 5.69; N, 7.88.

5e: 88% yield, mp 120—122 °C, colorless prisms. *Anal.* Calcd for $C_{22}H_{22}N_2O_3S$: C, 67.00; H, 5.58; N, 7.10. Found: C, 67.03; H, 5.63; N, 7.40.

3-Azaindolizines (Pyrazolo[2,3-*a*]pyridines) (6a—e)——General Procedure: Solid potassium carbonate (2—3 g) was added in small portions to a solution of a salt (**5**: 5—10 mmol) in dimethylformamide (5—10 ml) with stirring at room temperature. After stirring for an additional 5—6 h, water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The extract was dried over anhydrous K_2CO_3 and then concentrated *in vacuo*. The residue was chromatographed on silica gel with CH_2Cl_2 as an eluent to give the corresponding 3-azaindolizines (**6**) as yellow oils (except **6a**). No spectral data for the known compounds (**6a** and **6b**) were given in the literature, so their NMR spectral data are included below.

6a:[15] 38% yield. NMR δ: 6.36 (1H, d, 1-H), 6.58 (1H, dd, 6-H), 6.93 (1H, dd, 7-H), 7.37 (1H, d, 8-H), 7.78 (1H, d, 1-H), 8.29 (1H, d, 5-H), $J_{1,2}=2$, $J_{5,6}=7$, $J_{6,7}=7$, $J_{7,8}=9$ Hz.

6b: 75% yield. MS *m/e*: 132 (M^+). NMR δ: 2.48 (3H, s, 1-Me), 6.42 (1H, s, 1-H), 6.60 (1H, dd, 6-H), 7.00 (1H, dd, 7-H), 7.37 (1H, d, 8-H), 8.33 (1H, d, 5-H), $J_{1,2}=2$, $J_{5,6}=7$, $J_{6,7}=7$, $J_{7,8}=9$ Hz. *Anal.* Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.81; H, 6.06; N, 21.05.

6c: 65% yield. MS *m/e*: 174 (M^+). NMR δ: *n*-Bu [0.94 (3H, t, $J=8$ Hz), 1.2—1.9 (4H, m), and 2.82 (2H, t, $J=8$ Hz)], 6.21 (1H, s, 1-H), 6.50 (1H, dd, 6-H), 6.91 (1H, dd, 7-H), 7.30 (1H, d, 8-H), 8.30 (1H, d, 5-H), $J_{1,2}=2$, $J_{5,6}=7$, $J_{6,7}=7$, $J_{7,8}=9$ Hz. *Anal.* Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.77; H, 8.04; N, 15.98.

6d: 75% yield. MS *m/e*: 148 (M^+). NMR δ: 4.90 (2H, s, $C\underline{H}_2OH$), 5.9 (1H, br, OH), 6.38 (1H, s, 1-H), 6.44 (1H, dd, 6-H), 6.84 (1H, dd, 7-H), 7.22 (1H, d, 8-H), 8.20 (1H, d, 5-H), $J_{1,2}=2$, $J_{5,6}=7$, $J_{6,7}=7$, $J_{7,8}=9$ Hz. *Anal.* Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.61; H, 5.44; N, 18.84.

6e: 98% yield, mp 106—107 °C (lit.[15] mp 109 °C). NMR δ: 6.56 (1H, dd, 6-H), 6.64 (1H, s, 1-H), 6.92 (1H, dd, 7-H), 7.4 (5H, m, Ph-H), 7.93 (1H, d, 8-H), 8.38 (1H, d, 5-H), $J_{1,2}=2$, $J_{5,6}=7$, $J_{6,7}=7$, $J_{7,8}=9$ Hz.

2-Ethynylquinolines (11a—c), 1-Ethynylisoquinolines (14a—c), and 3-Ethynylisoquinolines (17a—c)——These compounds were prepared from 2-bromoquinoline, 1-bromoisoquinoline, or 3-bromoisoquinoline by the reported method.[16]

***N*-Amino-2-ethynylquinolinium Mesitylenesulfonates (12a—c)**——2-Ethynylquinolines (**11a—c**) were aminated and worked up as described for the preparation of **5** to give the salts (**12**).

12a: 93% yield, mp 118—119 °C, colorless prisms. *Anal.* Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.92; H, 6.60; N, 6.60. Found: C, 67.57; H, 6.60; N, 6.54.

12b: This compound was too hygroscopic to be purified, and thus it was used for the following reaction without purification.

12c: 95% yield, mp 79—81 °C, colorless prisms. *Anal.* Calcd for $C_{26}H_{24}N_2O_3S$: C, 70.27; H, 5.41; N, 6.30. Found: C, 70.13; H, 5.26; N, 6.03.

Pyrazolo[2,3-*a*]quinolines (13a—c)——The salts (**12**) were treated with K_2CO_3 in dimethylformamide and worked up as described for the preparation of **6** to give **13**.

13a: 78% yield, pale yellow oil, MS *m/e*: 224 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2$: C, 80.36; H, 7.14; N, 12.50. Found: C, 80.29; H, 7.11; N, 12.45.

13b: 32% yield (from **11b**). mp 94—95 °C, pale yellow prisms (from acetone–ether). MS *m/e*: 198 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.05; N, 14.14. Found: C, 72.64; H, 5.05; N, 14.06.

13c: 57% yield, mp 86—87 °C, pale yellow prisms (from benzene–*n*-hexane). MS *m/e*: 244 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_2$: C, 83.60; H, 4.92; N, 11.47. Found: C, 83.87; H, 4.84; N, 11.72.

***N*-Amino-1-ethynylisoquinolinium Mesitylenesulfonates (15a—c)**——1-Ethynylisoquinolines (**14a—c**) were aminated and worked up as described for the preparation of **5** to give the salts (**15**).

15a: 91% yield, mp 104—106 °C, colorless needles. *Anal.* Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.90; H, 6.60; N, 6.60. Found: C, 67.95; H, 6.52; N, 6.40.

15b: This compound was too hygroscopic to be purified, and thus it was used for the following reaction without purification.

15c: 92% yield, mp 123—124 °C, colorless prisms. *Anal.* Calcd for $C_{26}H_{24}N_2O_3S$: C, 70.25; H, 5.44; N, 6.30. Found: C, 70.34; H, 5.39; N, 6.29.

Pyrazolo[3,2-*a*]isoquinolines (16a—c)——The salts (**15a—c**) were treated with K_2CO_3 in dimethylformamide and worked up as described for the preparation of **6** to give **16**.

16a: 57% yield, mp 56—58 °C, pale yellow prisms (from *n*-hexane). MS *m/e*: 224 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2$: C, 80.36; H, 7.14; N, 12.50. Found: C, 80.30; H, 7.16; N, 12.30.

16b: 36% yield (from **14b**), mp 99—101 °C, pale yellow prisms (from acetone–ether). MS *m/e*: 198 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.05; N, 14.14. Found: C, 72.48; H, 5.09; N, 13.91.

16c: 67% yield, mp 115—116 °C, pale yellow prisms (from benzene–*n*-hexane). MS *m/e*: 244 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_2$: C, 83.60; H, 4.92; N, 11.47. Found: C, 83.65; H, 5.08; N, 11.36.

***N*-Amino-3-ethynylisoquinolinium Mesitylenesulfonates (18a—c)**——3-Ethynylisoquinolines (**17a—c**) were aminated and worked up as described for the preparation of **5** to give the salts (**18**).

18a: 85% yield, mp 93—94 °C, colorless needles. *Anal.* Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.92; H, 6.60; N, 6.60. Found: C, 67.97; H, 6.73; N, 6.56.

18b: 88% yield, mp 156—157 °C, colorless needles. *Anal.* Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.31; H, 5.56; N, 7.03. Found: C, 63.21; H, 5.50; N, 7.01.

18c: 90% yield, mp 152—153 °C, colorless prisms. *Anal.* Calcd for $C_{26}H_{24}N_2O_3S$: C, 70.25; H, 5.44; N, 6.30. Found: C, 70.19; H, 5.41; N, 6.36.

Pyrazolo[2,3-*b*]isoquinolines (19a—c)——The salts (**18a—c**) were treated with K_2CO_3 in dimethylformamide and worked up as described for the preparation of **6** to give **19**.

19a: 98% yield, mp 140—142 °C, yellow prisms (from acetone–ether). MS *m/e*: 224 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2$: C, 80.36; H, 7.14; N, 12.50. Found: C, 80.61; H, 7.19; N, 12.49.

19b: 46% yield, mp 166—168 °C, pale yellow prisms (from acetone–ether). MS *m/e*: 198 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.72; H, 5.05; N, 14.14. Found: C, 72.61; H, 4.83; N, 14.01.

19c: 82% yield, mp 159—160 °C, pale yellow prisms (from acetone–ether). MS *m/e*: 244 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_2$: C, 83.60; H, 4.92; N, 11.47. Found: C, 83.79; H, 4.77; N, 11.46.

References and Notes

1) Part II: T. Tsuchiya and H. Sashida, *Chem. Pharm. Bull.*, **29**, 1887 (1981).
2) W. J. McKillip, E. A. Sedor, M. B. Culbertson, and S. Wawzonek, *Chem. Rev.*, **73**, 255 (1973).
3) For reviews, see Y. Tamura, *Yakugaku Zasshi*, **100**, 1 (1980); Y. Tamura and M. Ikeda, "Advances in Heterocyclic Chemistry," Vol. 29, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, London, 1981, p. 71.
4) T. Tsuchiya, H. Sashida, and H. Sawanishi, *Chem. Pharm. Bull.*, **26**, 2880 (1978); and references cited therein.
5) For example, B. M. Trost and L. S. Melvin, Jr., "Sulfur Ylides," Academic Press, New York, 1975; W. Ando, *Acc. Chem. Res.*, **10**, 179 (1977); E. Vadejs, J. P. Hagen, B. L. Roach, and K. L. Spear, *J. Org. Chem.*, **43**, 1185 (1978); V. Cere, C. Paolucci, S. Pollicino, E. Sandri, and A. Fava, *ibid.*, **46**, 3315 (1981).
6) C. Kaneko, *Yuki Gosei Kagaku Kyokai Shi*, **26**, 758 (1968); G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).
7) For reviews, see T. Tsuchiya, *Yakugaku Zasshi*, **103**, 373 (1983); *idem, Yuki Gosei Kagaku Kyokai Shi*, **39**, 99 (1981); *idem, ibid.*, **41**, 641 (1983).
8) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, **1968**, 1083; A. Terada and Y. Kishida, *Chem. Pharm. Bull.*, **17**, 966 (1969).
9) J. C. Creig, N. N. Ekwuribe, and L. D. Grunke, *Tetrahedron Lett.*, **1979**, 4025; G. Hallström, B. Lindke, A. H. Khuthier, M. A. Al-Iraqi, *ibid.*, **1980**, 667.
10) H. Sashida and T. Tsuchiya, *Heterocycles*, **19**, 281 (1982).
11) A part of this work has been published in a preliminary communication: T. Tsuchiya and H. Sashida, *J. Chem. Soc., Chem. Commun.*, **1980**, 1109.
12) D. Leaver, W. K. Gibson, and J. D. R. Vass, *J. Chem. Soc.*, **1963**, 6053.
13) K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, **1975**, 4467.
14) Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, **1977**, 1; and references cited therein.
15) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, **1975**, 4506.
16) H. Yamanaka, M. Shiraiwa, K. Edo, and T. Sakamoto, *Chem. Pharm. Bull.*, **27**, 270 (1979).