4-BrPh), 127572-53-6; 7 (Y = 1-naphthyl), 127572-54-7; 7 (Y = $PhSO_2$), 127572-55-8; 7 (Y = formyl), 113169-27-0; 8 (Y = 4-MeOPh), 127572-56-9; 8 (Y = 4-BrPh), 127572-57-0; 8 (Y = Ph), 127572-58-1; 8 (Y = 3,4-$(MeO)_2$Ph), 127572-59-2; 8 (Y = 4-MePh), 127572-60-5; 8 (Y = 4-ClPh), 127572-61-6; 8 (Y = 4-NO_2Ph), 127572-62-7; 8 (Y = $PhSO_2$), 127572-63-8; $H_3CNHCH_2CO_2C_2H_5$·HCl, 52605-49-9; $H_2NCH_2CO_2C_2H_5$·HCl, 623-33-6; (phenylsulfonyl)acetic acid, 3959-23-7; *N*-benzyl-2-carbethoxy-4-formylpyrrole, 127572-64-9; *N*-benzylglycine ethyl ester, 6436-90-4; 2-iminovinamidinium, 127572-66-1.

Condensation of (2-Bromo-1-phenylethylidene)malononitrile with Substituted Thioureas: An Unusual Ring Size Effect

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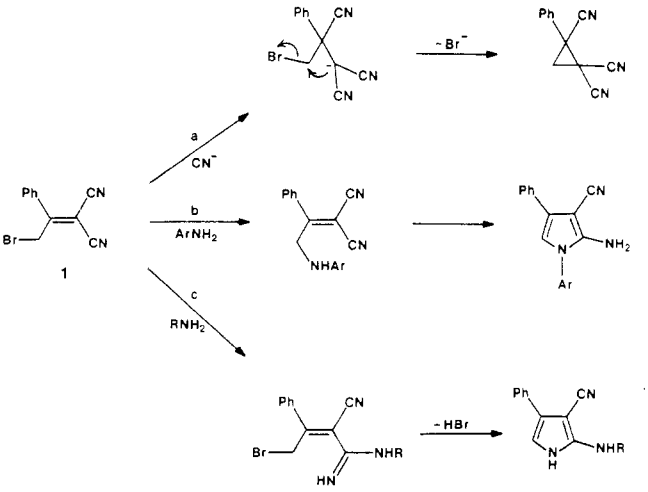
Condensations of the title electrophile with ambident S,N-nucleophiles, e.g., thiourea, *N,N'*-diphenylthiuourea, and thiosemicarbazide, proceed via initial S-alkylation followed by closure of the thiazole ring. In contrast to this, cyclic thioureas with the five-, six- and seven-membered rings afford distinct condensation products depending on the size of the ring. 2-Imidazolinethione gave 7-cyano-2,3-dihydro-5-mercapto-6-phenyl-1*H*-pyrrolo[1,2-*a*]-imidazole in low yield. 3,4,5,6-Tetrahydro-2(1*H*)-pyrimidinethione afforded [2-(1-isothiocyano-3-aminopropyl)-1-phenylethylidene]malononitrile in high yield, while 1,3,4,5,6,7-hexahydro-2*H*-1,3-diazepine-2-thione gave 7-amino-8-cyano-9-phenyl-2,3,4,5-tetrahydropyrido[1,2-*a*][1,3]diazepine in moderate yield. A common feature of these cyclizations is the primary S-nucleophilic attack, which was confirmed by isolation and characterization of the corresponding intermediates. The effects of ring size are discussed.

The reactions of (2-bromo-1-phenylethylidene)malononitrile (1)[1] with nucleophiles proceed via three main routes depending on the nature of the nucleophile.[2] With anions (RO^-, CN^-, BH_4^-) the reaction commences with addition to the double bond of 1 followed by cyclopropane ring closure (Scheme I, path a).[1a] With mildly basic amines ($ArNH_2$) S_N2 substitution of the bromine atom takes place followed by pyrrole ring closure (path b).[3] Alternatively, one of the cyano groups can be attacked by a more basic aliphatic amine (RNH_2; path c) to give rise to a differently substituted pyrrole.[3]

We have reported previously[4] that cyclic thioureas with five- and six-membered rings underwent distinct condensations with 1. Thus, 2-imidazolidinethione (2) and 1 gave the substituted pyrrolo[1,2-*a*]imidazole 3, while 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinethione (4) afforded the open-ring isothiocyanate 5 (Scheme II). In contrast to 2 and 4, thiourea reacted with 1 in a usual way to afford 2-amino-4-phenylthiazole (6). We suggested a mechanistic explanation for the formation of 3 and 6 based on an initial nucleophilic displacement by the sulfur in 2 or thiourea, respectively, of the reactive allylic bromine atom in 1. On the other hand, the formation of 5 pointed to an initial nucleophilic attack by one of the nitrogen atoms in 4, followed by base-induced opening of the tetrahydropyrimidine ring.

Scheme I



The apparent dichotomy in the S- versus N-nucleophilic reactivity of 2 and 4, respectively, is remarkable indeed, as cyclic thioureas are generally regarded as archetypal S-nucleophiles.[5,6] While the different nucleophilic sites in thiourea and 4 could be explained by alkyl substituent effects that increase the nucleophilicity of the nitrogen atoms, such an explanation cannot hold for the distinct behavior of 2 and 4 in which the substitution patterns at the nitrogens are nearly identical. The unusual dichotomy

(1) *Warning!* (2-Bromo-1-phenylethylidene)malononitrile is potent allergen.

(2) (a) Berg, A. S.; Kolsaker, P. *Acta Chem. Scand. B* **1980**, *34*, 289-293. (b) Storesund, H. J.; Kolsaker, P. *Tetrahedron* **1974**, *30*, 3153-3157. (c) Verhé, R.; De Kimpe, N.; De Buyck, L.; Courtheyn, D.; Van Caenegem, L.; Schamp, N. *Bull. Soc. Chim. Belg.* **1983**, *92*, 371-396.

(3) Gewald, K.; Hentschel, M. *J. Prakt.* Chem. **1976**, *318*, 663-670.

(4) Svetlik, J.; Turecek, F. *Tetrahedron Lett.* **1984**, *25*, 3901-3904.

(5) Bogatskii, A. V.; Lukyanenko, N. G.; Kirichenko, T. I. *Khim. Geterotsikl. Soedin.* **1983**, 723-737.

(6) For N- versus S-alkylation of substituted thioureas see: Coppola, G. M.; Shapiro, M. J. *J. Heterocycl. Chem.* **1981**, *18*, 495-497.

0022-3263/90/1955-4740$02.50/0

Scheme II

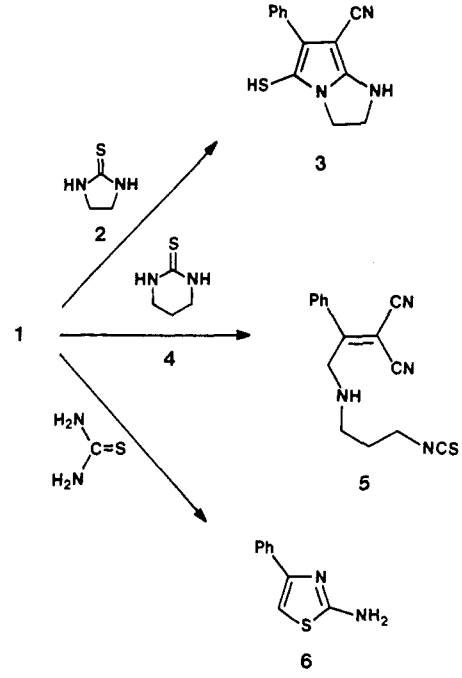
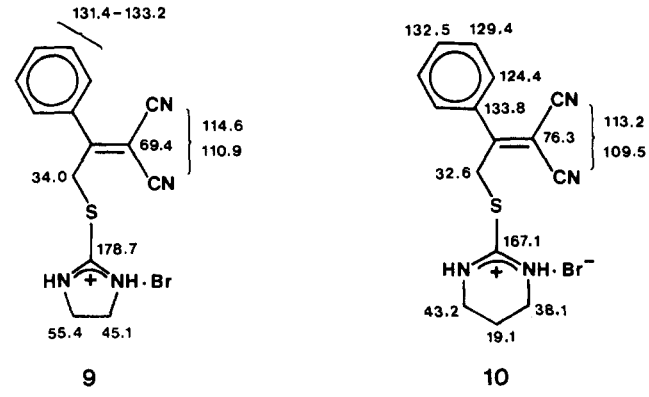


Chart I



in the alkylation of **2** and **4** is now addressed in this more detailed study aimed at answering the following questions: (1) Does nucleophilic attack proceed by distinct sites (S or N) with thioureas bearing different substituents at the nitrogen atoms? (2) What are the structural features that determine the further course of these condensations? To this end, we have investigated the reactions of **1** with other ambident S,N-nucleophiles, e.g., 1,3,4,5,6,7-hexahydro-2*H*-1,3-diazepine-2-thione (**7**), 3,4,5,6,7,8-hexahydro-1,3-diazocine-2(1*H*)-thione (**8**), *N*,*N*′-diphenylthiourea, and thiosemicarbazide.

Results

Reactions of Cyclic Thioureas. The condensations of **2** and **4** proceed in two separate steps.[4] Both these cyclic thioureas react rapidly with **1** in ethanolic solution in the absence of base to give crystalline, sparingly soluble, intermediates (**9** and **10**, respectively), which are further converted to the final products upon treatment with triethylamine. Combustion analyses demonstrate both the primary intermediates (**9** ($C_{14}H_{13}BrN_4S$) and **10** ($C_{15}H_{15}BrN_4S$) from **2** and **4**, respectively) to be hydrobromide salts corresponding to 1:1 adducts formed by nucleophilic substitution of the bromine atom in **1**. Hence, **9** and **10** appear to be the key intermediates whose structures might give the clue to the site of the initial nucleophilic attack. Unfortunately, ^{13}C NMR measurements revealed that, even in the absence of base, both **9** and **10** decomposed upon dissolution in D_2O, DMF-d_7, or DMSO-d_6, giving complex mixtures containing only traces of **3** and **5**, respectively. Since neither **9** nor **10** was soluble in other NMR solvents, we resorted to NMR measurements in the solid state.

The cross-polarization, magic angle spinning (CP MAS) ^{13}C NMR spectra of **9** and **10** are displayed in Chart I. The spectrum of **9** displayed the signal of the imino thiol quaternary carbon at the lowest field,[7] a poorly resolved multiplet of aromatic carbons, two signals for the cyano groups, two distinct signals of the imidazolidine methylenes, a high-field signal of the sp^2 carbon bearing the cyano groups,[4] and a signal at δ 34.0. The latter is indicative[8] of a CH_2S group, confirming that the imidazolidine ring and the (phenylethylidene)malononitrile moiety are linked by the sulfur atom.

The CP MAS ^{13}C NMR spectrum of **10** (Chart I) is closely analogous to that of **9**, also showing a high-field signal at δ 32.6 corresponding by its shift to a CH_2S methylene.[8] This reveals that in **10** the tetrahydropyrimidine and (phenylethylidene)malononitrile units are connected by a sulfur bridge. The S-alkylated structure **10** is further supported by the upfield shift of the pyrimidine quaternary carbon[7] ($\Delta\delta$ = +8.5 ppm relative to **4**) and, indirectly, by the absence of a signal for a CH_2N methylene that would have been expected to occur at about δ 60.0.[8] The signal of the sp^2 carbon bearing the phenyl group was not detected for both **9** and **10**. By comparison, the same carbon of **1** appears at δ 171.47 in the ^{13}C NMR spectrum measured in DMSO-d_6 solution but is absent in the CP MAS NMR spectrum, possibly because of a long relaxation time.

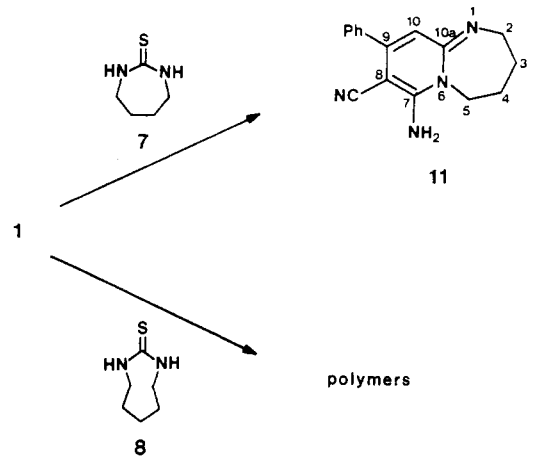
Further treatment of **9** and **10** with triethylamine in ethanol at reflux afforded **3** and **5**, respectively, in different yields. While **5** was formed almost quantitatively (95%), **9** gave only 15–20% of **3**. Other bases examined afforded even lower yields of **3**, e.g., Triton B (12%), 1,4-diazabicyclo[2.2.2]octane (8%), and pyridine (1%), or gave no isolable product (*sym*-collidine, 1,8-diazabicyclo[5.4.0]undec-7-ene). The major product from **9** (ca. 65%) was an ethanol-soluble polymer (mp >360 °C). Its electron impact mass spectrum showed dominant peaks of Br^+ and $HBr^{\bullet+}$ (m/z 79, 81 and 80, 82, respectively), indicating a hydrobromide salt. The fast atom bombardment (FAB) mass spectrum, obtained in a 3-nitrobenzyl alcohol matrix, gave two weak signals at m/z 242 (protonated **3**) and 294 (unidentified). The ^1H NMR spectrum showed two mutually coupled triplets at δ 4.22 and 4.80, a broad singlet for the phenyl group (δ 7.67), and two very broad, temperature- and concentration-dependent signals centered at δ 3.4 and 9.7. The IR spectrum showed a nitrile band at 2215 cm^{-1} and a very broad band of NH (2300–3600 cm^{-1}) with a shoulder at 3400 cm^{-1}. The spectral data, together with the absence of a CH_2S singlet in the ^1H NMR spectrum, suggest that the polymer is built of **3** subunits, although no more detailed structural information could be deduced.

The effect of ring size on the reactivity of cyclic thioureas was further studied for 1,3,4,5,6,7-hexahydro-2*H*-1,3-diazepine-2-thione (**7**) and 3,4,5,6,7,8-hexahydro-1,3-dia-

(7) Balestrero, R. S.; Forkey, D. M.; Russell, J. G. *Magn. Reson. Chem.* **1986**, *24*, 651–655 and references therein.

(8) (a) Barlin, G. B.; Brown, D. J.; Fenn, M. D. *Austr. J. Chem.* **1984**, *37*, 2391–2395. (b) Kalinowski, H.-O.; Berger, S.; Braun, S. *^{13}C-NMR-Spektroskopie*; Thieme; Stuttgart: 1984; pp 156, 164, and 165.

Scheme III



zocine-2(1*H*)-thione (**8**; Scheme III). The reaction of **7** with **1** in 2-propanol at reflux afforded a product identified by spectral data as 7-amino-8-cyano-9-phenyl-2,3,4,5-tetrahydropyrido[1,2-*a*][1,3]diazepine (**11**; Scheme III). The molecular formula ($C_{16}H_{16}N_4$; 264.1371 by high-resolution mass spectroscopy) pointed to a 1:1 condensation product after loss of hydrogen bromide and elemental sulfur. The infrared spectrum of **11** showed a broad band at 3400 cm^{-1} (NH_2) and bands corresponding to a nitrile (2200 cm^{-1}) and an exocyclic C=N bond (1650 cm^{-1}). The ^1H NMR spectrum displayed three methylene multiplets, a singlet for H-10, a narrow multiplet of the phenyl protons and a broad signal of the amino group. The chemical shift of the low-field methine is similar to that observed for the proton at the 3-position in substituted 2-iminopyridines.[9] The ^{13}C NMR spectrum displayed all 14 nonequivalent carbon signals. It is noteworthy that the magnitude of ^1J(C-10,H-10) agrees with the data reported for 1,2-dihydropyridines.[10] The formation of **11** shows that pentamethylenethiourea reacts in a way different from that of each of the lower homologues.

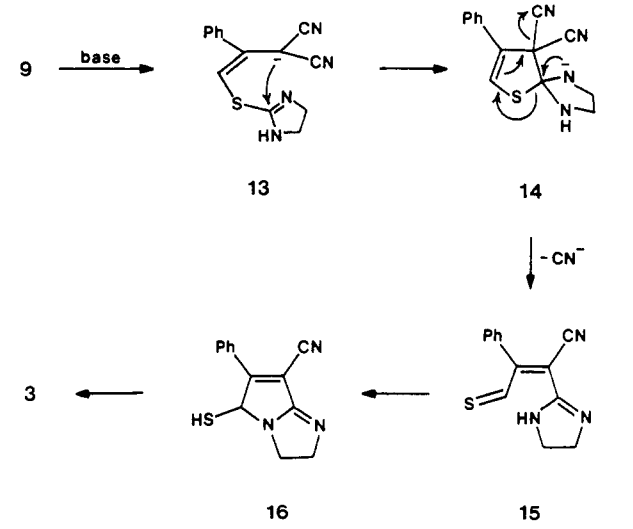
The reaction of **8** with **1** led to an untractable mixture of products, mainly due to base-induced polymerization of **1** or some intermediate. No reaction was observed in the absence of base. Thus, thiourea **8** appears to be much less reactive toward **1** than are the lower homologues **2**, **4**, and **7**.

Reactions of Acyclic S,N-Nucleophiles. In contrast to the cyclic thioureas, *N,N'*-diphenylthiourea and thiosemicarbazide react with **1** in a conventional manner,[4] affording 2-(phenylimino)-3,4-diphenylthiazoline (**12**) and 2-hydrazino-4-phenylthiazole, respectively, which were easily identified by their physical constants[11,12] and elemental analyses.

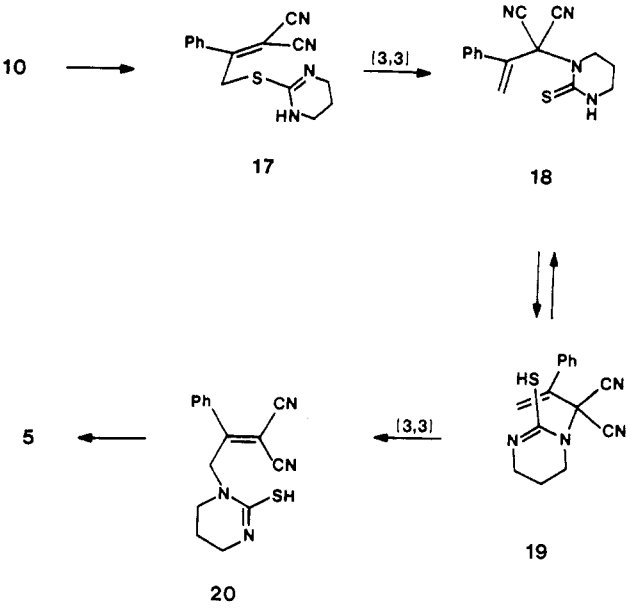
Discussion

The formation of the S-alkylated intermediates **9** and **10** in comparable yields shows that both **2** and **4** react as S-nucleophiles of comparable reactivity. The different outcomes of the condensations are therefore due to different reactivities of **9** and **10** upon treatment with base.[13]

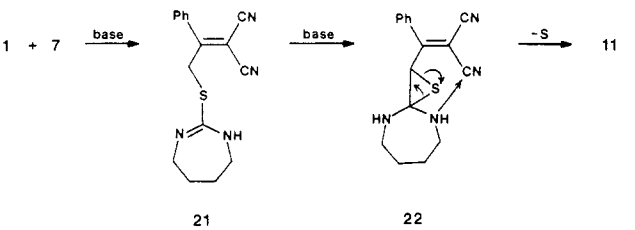
Scheme IV



Scheme V



Scheme VI

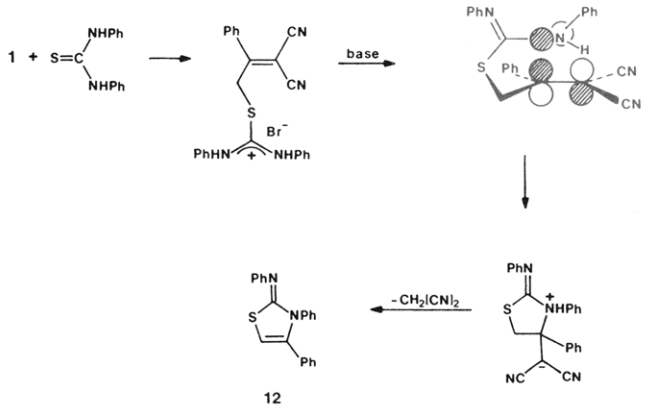


The reaction sequence from **9** to **3** is depicted in Scheme IV. The key step here is the formation of the C–C bond in anion **13**, followed by cyanide elimination, ring opening (**14**) and thione formation (**15**), pyrroline ring closure (**15** → **16**), and prototropic isomerization. A similar reaction sequence has been postulated recently for the condensation of **1** with *N*-thiocarbonylamidines.[15]

The formation of **5** from **10** requires cleavage of the CH_2–S bond and formation of a new CH_2–N bond. This can be visualized by a sequence of [3,3]-rearrangements

(9) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2089–2092.
(10) Vitorge, M. C.; Chenon, M. T.; Coupry, C.; Lumbroso-Bader, N. *Org. Magn. Reson.* **1983**, *21*, 20–23.
(11) Beyer, H.; Höhn, H.; Lässig, W. *Chem. Ber.* **1952**, *85*, 1122–1129.
(12) Hampel, W.; Müller, I. *J. Prakt. Chem.* **1969**, *311*, 684–686.
(13) A reviewer suggested that the different behavior of **9** and **10** may be due to their different acidities. The pK_{BH} values of *N,N'*-dialkylthioureas do show substituent effects,[14] while, to our knowledge, no data have been available for *S*-alkylisothioureas.
(14) Edward, J. T.; Lantos, I.; Derdall, G. D.; Wong, S. C. *Can. J. Chem.* **1977**, *55*, 812–821.
(15) Liebscher, J.; Pätzel, M.; Bechstein, U. *Synthesis* **1989**, 968–970.

Scheme VII



(17 → 18 and 19 → 20; Scheme V), combined with prototropic isomerization of 18 → 19. It should be noted that alternative mechanisms for the 17 → 20 isomerization cannot be excluded, e.g., 1,3-isomerization.[16]

The formation of 11 from 7 may be viewed as starting with S-alkylation, consistent with the reactions of the other thioureas (Scheme VI). Intermediate 21 then undergoes an Eschenmoser-type rearrangement[17] involving formation of thiirane 22, followed by extrusion of sulfur and cyclization via internal attack by the heterocycle nitrogen onto the nitrile group. Elemental sulfur was detected in the reaction mixture by mass spectrometry. This reaction sequence with sulfur extrusion is analogous to the condensation of heterocyclic thioamides with phenacyl halides or ethyl bromocyanoacetate.[18]

The different reactivities of the primary S-alkylation products 9, 10, and 21 are puzzling in view of the structural similarity of the heterocyclic moieties. Based on the overall yields of 3, 5, and 11, the [3,3]-rearrangement route leading to 5 should be preferred, although the low yields of 3 and 11 are in part due to polymerization of the intermediates or the products themselves.[19]

The reaction sequences leading to thiazoles 6 and 12 begin with S-alkylation in the same manner as with the cyclic thioureas. However, the further course of these cyclizations is different as the acyclic nucleophiles attack the polarized double bond of the α,α-dicyanoethylene moiety in a hetero-Michael addition that is terminated by elimination of malononitrile (Scheme VII). The cyclization, a 5-exo-Trig reaction,[20] is made possible by suitable orientation of the nitrogen lone-pair orbital with respect to the electrophilic terminus of the double bond in order to achieve favorable orbital overlap in the transition state. Such a favorable orientation can only be achieved by out-of-plane twist about the C(S,N)–N bond. However, the rotation is almost excluded in cyclic thioureas due to conformational restrictions imposed by the ring. Intramolecular hetero-Michael addition via a 5-exo-Trig process is therefore highly disfavored in 9, 10, and 21, consistent with the very different behavior of the cyclic and acyclic thioureas.

(16) (a) Singh, H.; Deep, K. *Tetrahedron* **1984**, *40*, 4937–4939. (b) Grout, R. J.; Partridge, M. W. *J. Chem. Soc.* **1960**, 3546–3557. (c) Assef, G.; Kister, J.; Metzger, J. *Bull. Soc. Chim. Fr. II* **1979**, 165–176.

(17) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710–734.

(18) (a) Singh, H.; Aggarwal, S. K.; Malhotra, N. *Indian J. Chem. Sect. B* **1983**, *22*, 99–100. (b) Singh, H.; Gandhi, C. S.; Bal, M. S. *Heterocycles* **1980**, *14*, 3–6.

(19) A reviewer suggested that an isothiocyanate analogue of 5 could have been formed from 9, while having been lost or undetected upon workup. However, the ^{1}H NMR and FAB mass spectra show no evidence for such a formation.

(20) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

Conclusion

Acyclic thioureas and thiosemicarbazide react with 1 in a uniform manner to give substituted thiazoles. The condensations proceed via initial S-alkylation followed by nucleophilic attack by the nitrogen atom at the electrophilic nitrile double bond. In cyclic thioureas, the latter step is prevented on stereoelectronic grounds and the further reactivity of the S-alkylated intermediates is controlled by the properties of the heterocyclic rings.

Experimental Part

Methods. Melting points (uncorrected) were determined on a Boetius micro hot-stage apparatus. IR spectra were measured on a Perkin-Elmer 377 spectrophotometer. Mass spectra were recorded on a Jeol D-100 double-focusing spectrometer (75 eV, 300 μA, 3 kV) using a direct-probe inlet. ^{1}H and ^{13}C NMR spectra were taken on a Varian XL-200 spectrometer (200.057 and 50.309 MHz for ^{1}H and ^{13}C, respectively). The chemical shifts (δ) were referenced to the residual signals of the solvent used. ^{13}C CP MAS NMR spectra were measured on a Varian VXR-300 spectrometer operating at 75.428 MHz for ^{13}C nuclei. The spectral width was 30 030 Hz. A total of 4096 data points were taken, which corresponded to resolution of 17.4 Hz/point. The CH_2 signal of adamantane at 37.8 ppm was used as external standard. The classical CP MAS experiment[21,22] was performed with 90° pulse on protons with duration of 8.5 μs. The cross-polarization was achieved in 29.4-kHz field for protons and carbons. Other parameters: mixing time, 2 ms; pulse repetition, 10 s; acquisition time, 60 ms with high-power decoupling (45 kHz); spinning rate, 4.03 kHz; 1000 transients. In order to distinguish between the protonated and nonprotonated carbons the "delay without decoupling" (DWD) technique[23] with 100-μs delay time was used. This delay allows one to dephase protonated carbons, and only nonprotonated ones are observed. To distinguish between signals and spinning sidebands, Dixon's TOSS pulse sequence[24] was used.

Preparations. S-Alkylation of Cyclic Thioureas. A solution of 1[25] (4 mmol, 1 g) in dry ethanol (10 mL) was added in one portion to a warm (50 °C) suspension of 2 or 4 (4 mmol) in ethanol (15 mL). After being stirred for 1 min, the solution was cooled to 25 °C and stirred at this temperature until the product separated (ca. 1–1.5 h). The white solid was then filtered off, washed thoroughly with acetone, and dried at reduced pressure.

[1-Phenyl-2-[(4,5-dihydroimidazol-2-yl)thio]ethylidene]malononitrile hydrobromide (9): yield 1.2 g (86%); mp 162–163 °C dec; IR (KBr) 3420, 2250, 1580, 1490, 1470, 1460, 1440 cm^{-1}; ^{13}C NMR spectrum is given in Chart I. Anal. Calcd for $C_{14}H_{13}BrN_4S$: C, 48.15; H, 3.75; Br, 22.88; N, 16.04; S, 9.18. Found: C, 48.40; H, 4.00; Br, 22.55; N, 15.81; S, 8.93.

[1-Phenyl-2-[(3,4,5,6-tetrahydropyrimidin-2-yl)thio]ethylidene]malononitrile hydrobromide (10): yield 1.1 g (76%); mp 174–177 °C dec; IR (KBr) 3420, 2250, 1630, 1530, 1440 cm^{-1}; ^{13}C NMR spectrum is given in Chart I. Anal. Calcd for $C_{15}H_{15}BrN_4S$: C, 49.59; H, 4.16; Br, 22.00; N, 15.42; S, 8.83. Found: C, 49.88; H, 4.40; Br, 21.73; N, 15.23; S, 8.55.

7-Amino-8-cyano-9-phenyl-2,3,4,5-tetrahydropyrido[1,2-*a*][1,3]diazepine (11). A warm solution of 1 (4 mmol, 1 g) in 2-propanol (15 mL) was added to a solution of 7[26] (4 mmol, 0.52 g) in 2-propanol (35 mL). 2-Propanol was used because 7 is not very soluble in ethanol. The mixture was stirred for 3 min and cooled rapidly to 20 °C, and triethylamine (4.6 mmol, 0.7 mL) was added dropwise. After being refluxed for 45 min, the reaction mixture was allowed to stand at room temperature for a few hours. The brown precipitate was filtered off, washed with water and ether, and dried to give 0.33 g (31%) or 21, mp 240–245 °C. An analytical sample was obtained by crystallization from acetone:

(21) Andrew, E. R. *Philos. Trans. Soc. (London)* **1981**, *A299*, 505.

(22) Mehring, M. *Principles of High Resolution NMR in Solids*; Springer: Berlin, 1983.

(23) Munowitz, M. G.; Griffin, R. G.; Bodenhausen, G.; Huang, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 2529–2533.

(24) Dixon, W. T. *J. Magn. Reson.* **1985**, *64*, 332–333.

(25) Gewald, K. *Chem. Ber.* **1965**, *98*, 3571–3577.

(26) Behringer, H.; Meier, H. *Justus Liebigs Ann. Chem.* **1957**, *607*, 67–91.

mp 246–247 °C; IR (KBr) 3400, 3307, 3193, 2207, 1653, 1617, 1560 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.00 (m, 4 H, 2 CH_2), 3.67 (m, 2 H, CH_2), 4.31 (m, 2 H, CH_2), 6.47 (s, 1 H, H-10), 7.60 (m, 5 H, ArH), 8.70 (br s, 2 H, NH_2); ^{13}C NMR (DMSO-d_6) δ 22.35 (t, CH_2), 22.81 (t, CH_2), 45.77 (t, CH_2), 51.16 (t, CH_2), 81.26 (sd, ^3J = 7.9 Hz, C-8), 100.97 (d, ^1J = 173 Hz, C-10), 115.96 (s, CN), 127.88, 129.09, 130.63, 135.59 (ArC, o, m, p, ipso), 155.46 (sm, C-7), 155.68 (sdd, ^2J and ^3J = 2.5 Hz, C-9), 158.17 (sm, C-10a). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.52; H, 5.95; N, 21.13.

2-(Phenylimino)-3,4-diphenylthiazoline (12). To a warm solution (50 °C) of *N,N'*-diphenylthiourea (Aldrich; 4 mmol, 0.912 g) in dry ethanol (30 mL) was added in one portion a solution of 1 (4 mmol, 1 g). The yellow reaction mixture was stirred at this temperature for 10 min and cooled to 25 °C, and triethylamine (4 mmol, 0.7 mL) in ethanol (3 mL) was added. The dark solution was refluxed for 45 min and then kept at room temperature for a few hours. The separated needles were filtered off and washed with water and ether to give 0.36 g (28%) of **12**, mp 191–196 °C. An analytical sample was obtained by recrystallization from ethanol; mp 195–196 °C (lit.[12] mp 192 °C).

2-Hydrazino-4-phenylthiazole. To a warm solution (50 °C) of thiosemicarbazide in DMF (10 mL) was added at once a solution of 1 (4 mmol, 1 g) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at this temperature for 5 min and cooled to 25 °C, and triethylamine (4.0 mmol, 0.7 mL) in ethanol (3 mL) was added dropwise over 5 min. After being heated at 50 °C for 45 min, the dark solution was poured into ice water (150 mL). The white crystalline material was filtered off by suction, washed with ether, and dried to afford 0.45 g (57%) of 2-hydrazino-4-phenylthiazole, mp 167–168 °C (ethanol) (lit.[11] mp 169 °C). The spectral data of our product were in good agreement with those of an authentic sample prepared according to ref 11.

A General Approach to the Synthesis of 1,6-, 1,7-, and 1,8-Naphthyridines[1]

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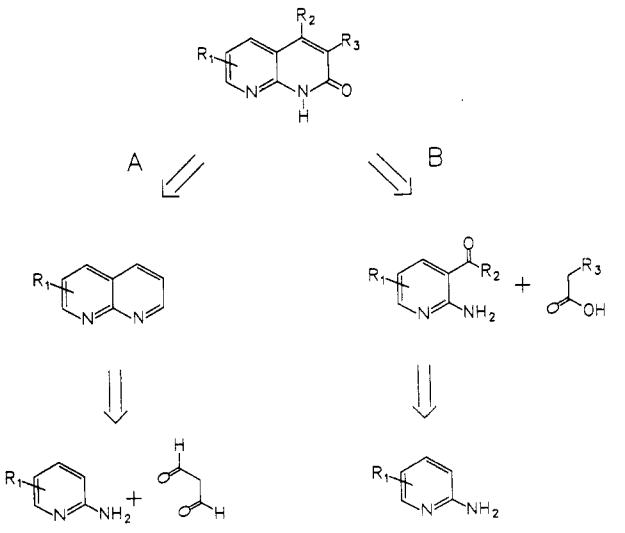
A new three-step procedure for pyridine annulation is described and illustrated with efficient syntheses of various 1,6-, 1,7-, and 1,8-naphthyridin-2-ones as well as 6-chloroquinolin-2-one. The regiospecific ortho metalation and subsequent formylation of 2-, 3-, or 4-(pivaloylamino)pyridines provides the corresponding protected ortho aminopyridinecarboxaldehydes as key intermediates in this procedure. After condensation of these aldehydes with *tert*-butyl lithioacetate the resulting β-hydroxy esters are treated with refluxing aqueous HCl to generate the naphthyridine system in excellent yield. Naphthyridines with diverse substitution patterns in either of the pyridine rings are available by appropriate modification of the overall pyridine annulation sequence.

The 1,*X*-naphthyridines (pyridopyridines) are deceptively simple members of the diazanaphthalene series.[2] In contrast to other heterocycles in this group (e.g., quinazolines and quinoxalines), the naphthyridines have attracted relatively little synthetic attention and, perhaps as a consequence, have only occasionally been used as substrates for biologically active molecules.[3] As part of continuing studies in our laboratory[4] we recently required a series of specifically substituted, yet previously unknown, 2-chloro-1,*X*-naphthyridines. We envisioned that our targeted materials would be readily available by dehydrative chlorination of the corresponding 1,*X*-naphthyridin-2-ones and thus set as our goal the development of methodology which would be widely applicable to the synthesis of the latter.

Retrosynthetic analysis of a 1,*X*-naphthyridin-2-one (Scheme I) suggested two approaches from readily available aminopyridines. Each route has parallels in quinoline chemistry[5] and both methods have been applied to the synthesis of various naphthyridines. In the first (route A),

Scheme I



a variant of which is directly analogous to the Skraup reaction, an electrophilic aromatic substitution is employed to elaborate the second ring. The well-known difficulty of pyridines to undergo such a reaction has limited this approach to those systems in which the starting pyridine is either unsubstituted or functionalized with electron-donating substituents.[2a,6]

(1) Presented in part at the 10th International Congress of Heterocyclic Chemistry; August, 1985; Waterloo, Ontario.

(2) For recent reviews see: (a) Paudler, W. W.; Sheets, R. M. *Adv. Heterocycl. Chem.* **1983**, *33*, 147. (b) Wozniak, M.; van der Plas, H. C. *Heterocycles* **1982**, *61*, 318.

(3) A notable exception is the series of pyridonecarboxylic acid antibiotics related to nalidixic acid. For leading references see: (a) Parikh, V. D.; Fray, A. H.; Kleinman, E. F. *J. Heterocycl. Chem.* **1988**, *25*, 1567. (b) Miyamoto, T.; Egawa, H.; Shibamori, K.; Matsumoto, J. *J. Heterocycl. Chem.* **1987**, *24*, 1333.

(4) Turner, J. A. U. S. Patent 4,472,193, 1984; U. S. Patent 4,533,381, 1985; U. S. Patent 4,536,208, 1985.

(5) Jones, G. In *Quinolines*; Jones, G., Ed.; John Wiley: New York, 1977; Part I, Chapter 2.

(6) For a successful example of the use of this approach for preparation of 1,5-naphthyridine see: Hamada, Y.; Takeuchi, I. *Chem. Pharm. Bull.* **1971**, *19*, 1857.

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