Notes

Electrochemical Synthesis Of *N*-Acetyl-2,3-substituted Pyrroles[1]

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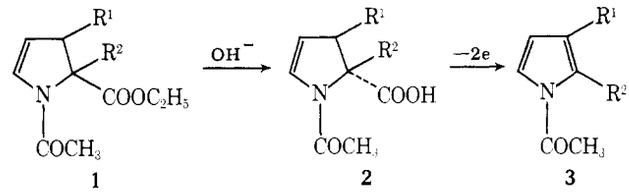
2,3-Substituted pyrroles are of physiological interest.[2] These pyrroles have been synthesized mainly by Knorr condensation of aminocarbonyl compounds or their precursors and carbonyl or dicarbonyl compounds;[3,4] the carbonyl compounds, however, are available with difficulty. Although a synthetic route to these pyrroles from aminonitrile and cinnamaldehyde, a so-called Miller–Plöchl condensation, has also been reported,[5] drastic conditions are required in the elimination step to the pyrroles. We now wish to report a convenient synthesis of *N*-acetyl-2,3-substituted pyrroles by anodic decarboxylation of *N*-acetyl-2,3-substituted-Δ^4-pyrroline-2-carboxylic acids, which are readily available. In previous reports from this laboratory, anodic oxidation, especially the abnormal Kolbe reaction,[6-8] has been investigated and shown to be of great preparative significance in the replacement of carboxylic acids by methoxy[9] or acetoxy[1] groups.

A synthesis of the pyrroles was carried out according to Scheme I. *N*-Acetyl-2,3-substituted-2-ethoxycarbonyl-Δ^4-pyrrolines **1a–d** were easily prepared by the reported methods;[10-12] diethyl acetamidomalonate and α,β-unsaturated aldehydes were condensed in ethanol in the presence of a catalytic amount of sodium ethoxide, followed by dehydration with *p*-toluenesulfonic acid. Saponification of the compounds (**1a–d**) gave the corresponding *N*-acetyl-2,3-substituted-Δ^4-pyrroline-2-carboxylic acids **2a–d** in good yields; the NMR spectra[11,12] of the compounds obtained herein showed that 2-carboxylic acids are trans to 3-substituents.

Anodic oxidation of compounds **2a–d** was carried out at 5–10 °C in a nondivided cell by the use of a graphite anode–graphite cathode. On electrolysis of compounds **2a–d** in water–tetrahydrofuran (3:1) using 0.05 molar equiv of potassium hydroxide, pyrroles **3a–d** were obtained in 86–94% yield. The products due to thermal decarboxylation of compounds **2a–d** were not observed under the electrolysis conditions. The use of a platinum anode gave almost the same result as that of the graphite anode. The current efficiencies of these electrode reactions were approximately 100%. The yields and electrolysis conditions are summarized in Table I. The *N*-acetylpyrroles **3a–d** thus obtained were easily hydrolyzed with aqueous ethanol containing sodium bicarbonate to give the deacetylated pyrroles.

Scheme I



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a, R^1 = Ph; R^2 = $COOC_2H_5$
b, R^1 = Ph; R^2 = H
c, R^1 = CH_3; R^2 = $COOC_2H_5$
d, R^1 = CH_3; R^2 = H

Simultaneous oxidation of the electrolysis products is frequently encountered in anodic oxidation of organic compounds. It has been well documented that pyrroles are anodically oxidized at a relatively low potential to show a complicated product distribution; the products are usually 2,5-substituted-Δ^3-pyrrolines,[13] 2-*H*-pyrroles,[14] etc. Although a variety of solvent–electrolyte systems have been examined to avoid further oxidation of the products in these electrolyses, only the water–tetrahydrofuran system employed here enabled the reactions to proceed smoothly without any side reactions, even with 1.5 times a theoretical amount of current. When, for example, the oxidation was carried out in water–acetonitrile or acetonitrile, the electrolyzed solution became dark brown presumably because of the concurrent oxidation of the products. Furthermore, the addition of an inorganic salt such as sodium sulfate or sodium perchlorate made the product distribution more complex.

Although the stabilization of the carbonium ion by an acylamino group is responsible for the formation of only substitution products in the anodic oxidation of substituted acylaminomalonic acid monoester,[1,9] the electrolysis of *N*-

Table I. Electrolyses Conditions and Product Yields[a]

Run	Substrated (mmol)	Anode material[b]	Electrolyte[c]	Current density, mA/cm²	Amount of electricity, F/mol	Product (yield, %)
1	**2a** (10)	C	A	100	2.0	**3a** (91)
2	(10)	C	B	100	3.0	(91)
3	(10)	Pt	A	100	2.0	(94)
4	(100)	C	A	100	2.0	(90)
5	**2b** (10)	C	A	50	2.0	**3b** (86)
6	(10)	C	B	50	3.0	(41)[d]
7	**2c** (10)	C	A	100	2.0	**3c** (92)
8	(10)	C	B	100	3.0	(80)
9	**2d** (10)	C	A	100	2.0	**3d** (93)
10	**4** (3)	C	B	100	2.0	**5** (98)[e]

[a] The electrolysis was carried out at 5–10 °C in a nondivided cell. [b] C, carbon electrode and Pt, platinum electrode. [c] A, water–tetrahydrofuran (3:1) containing 0.05 molar equiv of potassium hydroxide to that of the substrate (**2a–d**); B, methanol containing 0.05 molar equiv of sodium methoxide to that of the substrate (**2a–c, 4**). [d] Compound **6** as well as the main product **3b** was isolated in 4.5% yield. [e] Mixture of *cis*-**5a** and *trans*-**5b** isomers.

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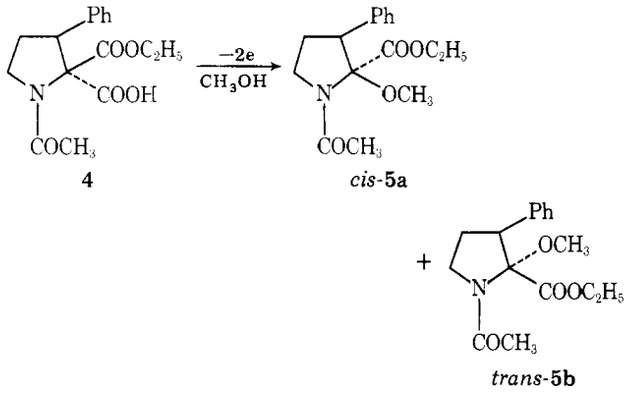
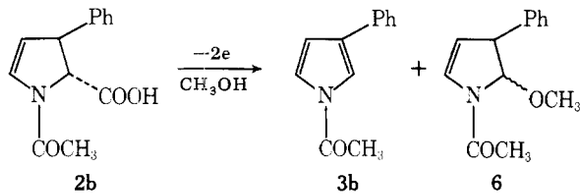
Scheme II



Scheme III



acetyl-Δ^4-pyrroline-2-carboxylic acids in this system gave no substitution products but only elimination products, pyrroles. However, even if *N*-acetyl-2-hydroxy-Δ^4-pyrroline, which is considered to be a substitution product, was formed in this electrolysis, this compound would be transformed spontaneously into the pyrrole by elimination of water. Accordingly, in order to examine the real electrode reaction, the electrolysis was carried out in methanol; the methoxylated products would be stable and isolated by the workup procedure employed here. Compound **2a** was electrolyzed in methanol containing 0.05 molar equiv of sodium methoxide, and the corresponding pyrrole **3a** was obtained in 91% yield. Careful analysis of the electrolysis product showed that the substitution product did not form. This result indicates that the lifetime of the carbonium ion generated by anodic oxidation of **2a** in a methanol or water–tetrahydrofuran (3:1) system is too short to enable solvent capture to compete with elimination; the driving force for elimination is aromatization. In fact, the products in the electrolysis of *cis*-*N*-acetyl-2-ethoxycarbonyl-3-phenylpyrrolidine-2-carboxylic acid (4) were those by substitution, which are a mixture of *cis*- and *trans*-*N*-acetyl-2-ethoxycarbonyl-2-methoxy-3-phenylpyrrolidines (Scheme II); these two isomers were assigned based on NMR spectra in which the chemical shift of the ester group CH_2CH_3 of compound **5a** (cis form) falls at a considerable lower field than that of compound **5b** (trans form). Furthermore, in the electrolysis of compound 2b in which the reaction would proceed via the carbonium ion possessing a longer lifetime than that of 2a, a small amount of substitution product **6** (4.5%) was formed, although the predominant formation of pyrrole **3b** was also observed (Scheme III); methoxy compound **6** was stable to the reaction and workup conditions.

In the electrolysis in water–tetrahydrofuran or methanol, the electrode reaction is initiated by an electron transfer from the carboxylate of compounds **2a–d** to the anode; the products due to oxidation of the allylic[15,16] or benzylic positions[17,18] of compounds **2a–d** were not observed.

Experimental Section

Equipment. Melting points were measured using the Yamato melting point apparatus and were uncorrected. IR spectra were recorded on a Schimadzu IR-27G infrared spectrophotometer. NMR spectra were obtained using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as an internal standard. Electrolysis was carried out by use of a Hokuto HA 104 (1 A–55 V) potentio–galvanostatt attached to a Hokuto HA 108A coulomb meter.

Preparation of *N*-Acetyl-Δ^4-pyrroline-2-carboxylic Acids 2a–d. Compounds **2a** and **2c** were prepared as follows. Diester **1a** or **1c**[11,12] (0.1 mol) was dissolved in 70 mL of ethanol. To this was added dropwise a solution of potassium hydroxide (0.11 mol) dissolved in 20 mL of ethanol containing 6 mL of water at 20–25 °C under vigorous stirring. The reaction mixture was allowed to stand at ambient temperature for 3 days, and then the solvent was evaporated under reduced pressure below 30 °C. The residue was dissolved in 10–30 mL of water, and the solution was washed with ethyl acetate. The aqueous layer was acidified to Congo red with 12 N hydrochloric acid at 0 °C. The acidified solution was shaken with three 100-mL portions of ethyl acetate, and the combined ethyl acetate layer was washed twice with 20 mL of water, dried over magnesium sulfate, and then evaporated to dryness in vacuo below 30 °C. The resulting crystals were recrystallized with ethyl acetate–*n*-hexane. This procedure led to the saponification of only the ester group trans to the 3-substituents.

Compound **2a** (mp 106–107 °C) was obtained in 98% yield. The spectral and analytical data are as follows: IR (Nujol) 1745, 1735, 1590 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.85 (t, 3 H), 2.30 (s, 3 H), 3.54 (q, 2 H), 5.10 (t, 1 H, J = 2 Hz), 5.36 (dd, 1 H, J = 2, 5 Hz), 6.82 (dd, 1 H, J = 2, 5 Hz), 7.28 (s, 5 H). Anal. Calcd for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.25; H, 5.61; N, 4.55.

Saponification of compound **1c** afforded mono ester **2c** (mp 62–63 °C) in 78% yield: IR (Nujol) 1745, 1730, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, 3 H), 1.28 (t, 3 H), 2.24 (s, 3 H), 3.6–4.1 (m, 1 H), 4.28 (q, 2 H), 5.22 (dd, 1 H, J = 3, 5 Hz), 6.50 (dd, 1 H, J = 3, 5 Hz), 12.0 (broad s, 1 H). Anal. Calcd for $C_{11}H_{15}O_5N$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.71; H, 6.29; N, 5.80.

Saponification of compound **1b**[12] under the same conditions as above gave *trans*-**2b** (78%), mp 184–186 °C (lit.[12] mp 187–189 °C); *trans*-**2d** was similarly prepared from compound **1d** in 82% yield: mp 120–121 °C; IR (Nujol) 3120, 1740, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (d, 3 H), 2.20 (s, 3 H), 2.9–3.4 (m, 1 H), 4.38 (m, 1 H), 5.20 (dd, 1 H, J = 3, 5 Hz), 6.48 (dd, 1 H, J = 3, 5 Hz), 10.05 (broad s, 1 H). Anal. Calcd for $C_8H_{11}O_3N$: C, 56.79; H, 6.55; N, 8.38. Found: C, 56.88; H, 6.66; N, 8.23.

General Electrolysis Procedure. The electrolysis cell used was an ordinary beaker as reported previously.[1] The compound (**2a–d**) (0.01 mol) was dissolved in a mixture of 15 mL of tetrahydrofuran and 5 mL of water containing 0.15 mL of 1 N potassium hydroxide. The solution was put in the electrolysis cell and electrolyzed under the conditions described in Table I. When a theoretical amount of electricity was passed, the starting material was completely consumed. The electrolyzed solution was concentrated to dryness in vacuo below 30 °C. The residue was extracted with ethyl acetate. The extract was washed once with water, dried over magnesium sulfate, and then concentrated to dryness in vacuo. Compounds **2a** and **2b** were recrystallized from ethyl acetate–*n*-hexane. Compounds **2c** and **2d** were purified by distillation under reduced pressure.

Electrolysis in methanol was carried out under the same conditions described above, except that sodium methoxide was used as an electrolyte instead of potassium hydroxide.

Compound 3a. Compound **2a** was electrolyzed in water–tetrahydrofuran (3:1) or methanol to afford the titled compound: mp 52–53 °C; IR (Nujol) 1730, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.52 (s, 3 H), 4.29 (q, 2 H), 6.38 (d, 1 H), 7.14 (d, 1 H), 7.2–7.7 (m, 5 H); MS *m/e* 257 (M^+). Anal. Calcd for $C_{15}H_{15}O_3N$: C, 69.98; H, 5.82; N, 5.53. Found: C, 70.02; H, 5.88; N, 5.44.

Compound **2a** was also oxidized using a platinum anode to afford compound **3a**, the physical constants being identical with those described above.

Compound **3a** (0.92 g) obtained above was suspended in 10 mL of water saturated with sodium bicarbonate, and the suspension was vigorously stirred at room temperature for 3 days. The reaction mixture was shaken with ethyl acetate, and the ethyl acetate layer was dried over magnesium sulfate. The solvent was evaporated to dryness in vacuo. The resulting crystals were recrystallized with ethyl acetate–*n*-hexane. This procedure allowed the quantitative formation of the deacetylated compound 2-ethoxycarbonyl-5-phenylpyrrole, mp 67–68 °C (lit.[19] mp 66–67 °C). Anal. Calcd for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.15; H, 6.17; N, 6.31.

Compound 3b. Compound **2b** was decarboxylated anodically in water–tetrahydrofuran (3:1) to afford compound **3b:** mp 87–89 °C; IR (Nujol) 1710, 1610, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (s, 3 H), 6.5–6.7 (m, 1 H), 7.1–7.7 (m, 7 H); MS (intensity) *m/e* 185 (M^+, 41), 143 (base peak), 115 (36), 43 (23). Anal. Calcd for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.59. Found: C, 77.61; H, 5.99; N, 7.43.

When compound **2b** was electrolyzed in methanol, the electrolyzed solution became dark brown. The solution showed several spots on TLC. The main products were isolated by silica gel chromatography using chloroform–ethyl acetate (9:1) as eluate. These were compounds **3b** (41%) and **6** (4.5%). The physical constants of compound **3b** obtained here were in complete agreement with those described above. Compound **6** (syrup) was a mixture of cis and trans isomers: NMR ($CDCl_3$) δ 2.14 and 2.24 (s and s, 3 H), 3.55 and 3.52 (s and s, 3 H), 3.8–4.0 and 4.0–4.2 (m and m, 1 H), 5.1–5.5 (m, 2 H), 6.6–7.6 (m, 6 H). The ratio of these isomers is 7:6 (cis/trans).

Compound 3c. Electrolysis of compound **2c** gave the titled compound: bp 99–100 °C (1 mm); IR (film) 3150, 1740–1710 (broad) cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.22 (s, 3 H), 2.48 (s, 3 H), 4.33 (q, 2 H), 6.05 (d, 1 H), 7, 12 (d, 1 H); MS (intensity) 185 (M^+, 41), 143 (base peak), 115 (36), 43 (23). Anal. Calcd for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.33; H, 6.43; N, 7.01.

Compound 3d. Anodic oxidation of compound **2d** afforded the titled compound: bp 41–42 °C (2 mm); IR (film) 3050, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.45 (s, 3 H), 6.0–6.2 (m, 1 H), 6.9–7.1 (m, 1 H), 7.1–7.3 (m, 1 H); MS (intensity) 123 (M^+, 26), 97 (10), 81 (43), 80 (base peak), 53 (18), 43 (48). Anal. Calcd for C_7H_9ON: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.31; H, 7.32; N, 11.31.

Preparation of *cis*-4. *N*-Acetyl-2,2-diethoxycarbonyl-3-phenylpyrrolidine[12] was saponified with potassium hydroxide under the same conditions as described above to afford the title compound in 49% yield; this was recrystallized from ethyl acetate–*n*-hexane: mp 97–99 °C; IR (Nujol) 1740, 1720, 1620, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.01 (t, 3 H), 2.22 (s, 3 H), 2.0–2.9 (m, 2 H), 3.5–4.5 (m, 3 H), 3.88 (q, 2 H), 7.35 (s, 5 H). Anal. Calcd for $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.94; H, 6.23; N, 4.56.

Electrolysis of *cis*-4. After compound 4 (910 mg) was electrolyzed under the conditions as shown in Table I, the electrolyzed solution was neutralized by the addition of acetic acid, and the solvent was evaporated to dryness in vacuo. The resulting residue was extracted with ethyl acetate, and the solution was washed with water, dried over magnesium sulfate, and then evaporated to dryness in vacuo. The residue was treated with silica gel chromatography using chloroform–ethyl acetate (5:4) as eluate to afford 460 mg of *cis*-**5a** and 420 mg of *trans*-**5b**.

Compound 5a: mp 130–131 °C; NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.10 (s, 3 H), 2.0–3.0 (m, 2 H), 3.35 (s, 3 H), 3.5–3.8 (m, 3 H), 4.22 and 4.24 (q, 2 H), 7.25 (s, 5 H). Anal. Calcd for $C_{16}H_{21}O_4N$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.74; H, 7.14; N, 4.76.

Compound **5b** (syrup): NMR ($CDCl_3$) δ 0.81 and 0.89 (t and t, 3 H), 1.98 and 2.15 (s and s, 3 H), 2.0–3.0 (m, 2 H), 3.46 (s, 3 H), 3.72 and 3.79 (q and q, 2 H), 3.4–4.5 (m, 3 H), 7.1–7.4 (m, 5 H). Anal. Calcd for $C_{16}H_{21}O_4N$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.89; H, 7.31; N, 4.93.

The separation of the NMR signals of each group observed above is attributed to the rotational barrier about the C–N bond.[20]

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Registry No.—**2a,** 64163-63-9; **2b,** 51212-32-9; **2c,** 64163-64-0; **2d,** 64163-65-1; **4,** 64163-66-2; **3a,** 64163-67-3; **3b,** 64163-68-4; **3c,** 64163-69-5; **3d,** 823-75-6; **1a,** 51212-30-7; **1b,** 64163-70-8; **1c,** 5846-04-8; **1d,** 64163-71-9; **5a,** 64175-43-5; **5b,** 64163-72-0; *cis*-**6,** 64163-73-1; *trans*-**6,** 64163-74-2; 2-ethoxycarbonyl-5-phenylpyrrole, 13355-43-6; *N*-acetyl-2,2-diethoxycarbonyl-3-phenylpyrrolidine, 51212-36-3.

References and Notes

(1) Synthetic Electroorganic Chemistry. VII. Part VI: T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, *J. Org. Chem.*, **42,** 2419 (1977).
(2) K. Tanaka, K. Kariyone, and S. Umino, *Chem. Pharm. Bull.*, **17,** 611 (1969), and references cited therein.
(3) E. Baltazzi and L. I. Krimen, *Chem. Rev.*, **63,** 511 (1963), and references cited therein.
(4) J. M. Patterson, *Synthesis*, 281 (1976), and references cited therein.
(5) V. A. Treibs and R. Derra, *Justus Liebigs Ann. Chem.*, **589,** 176 (1954).
(6) L. Everson, in "The Chemistry of Carboxylic Acids and Esters", S. Patai, Ed., Interscience New York, N.Y., 1969, p 53.
(7) J. T. Keating and P. S. Skell, *Carbonium Ions*, **2,** 573 (1976).
(8) S. D. Ross, M. Finkelstein, and E. J. Rudd, "Anodic Oxidation", Academic Press, New York, N.Y., 1975, p 134.
(9) H. Horikawa, T. Iwasaki, K. Matsumoto, and M. Miyoshi, *Tetrahedron Lett.*, 191 (1976).
(10) D. A. Cox, A. W. Johnson, and A. B. Mauger, *J. Chem. Soc.*, 5024 (1964).
(11) A. B. Mauger, F. Irreverre, and B. Witkop, *J. Am. Chem. Soc.*, **88,** 2019 (1966).
(12) R. Sarges and J. R. Tretter, *J. Org. Chem.*, **39,** 1710 (1974).
(13) N. L. Weinberg and H. R. Weinberg, *Chem. Rev.*, **68,** 449 (1968).
(14) M. Libert, C. Caullet, and S. Longchamp, *Bull. Soc. Chim. Fr.*, 2376 (1971).
(15) T. Shono and A. Ikeda, *J. Am. Chem. Soc.*, **94,** 7802 (1972).
(16) T. Shono, A. Ikeda and Y. Kimura, *Tetrahedron Lett.*, 3599 (1971).
(17) S. H. Pines, *J. Org. Chem.*, **38,** 3854 (1974).
(18) L. Eberson and H. Schäfer, *Fortscr. Chem. Forsch.*, **21,** Chapters 7 and 9 (1971).
(19) S. Umino, K. Kariyone, K. Tanaka, and Noguchi, *Chem. Abstr.*, **70,** 57622 (1969); Japan Patent 24417 (1968).
(20) P. A. Bovey, "High-Resolution NMR of Macromolecules," Academic Press, New York, N.Y., 1972, Chapter XIII.

Thiocarbonyl Transfer Reagents[1]

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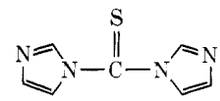
Heterocyclic thiocarbonyl transfer reagents, first prepared by Staab and co-workers,[3] have in the recent years found several important applications in the synthesis of new compounds.[4,5] Among these reagents mainly 1,1′-thiocarbonyldiimidazole (**1**) has been used, though reactions involving the



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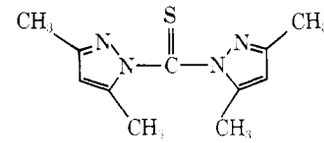

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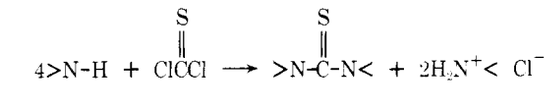
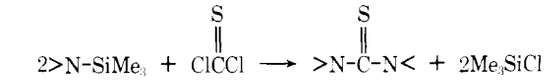
use of 1,1′-thiocarbonylbis(3,5-dimethylpyrazole) (**2**) also have been reported.[6]

Very little attention has been paid to the other members of this series, including 1,1′-thiocarbonyldibenzimidazole (**3**), 1,1′-thiocarbonyldibenzotriazole (**4**), and thiocarbonyldiindazole (**5**). Compounds **1** and **2** have been prepared in excellent yield[3,6] according to the following reaction. Compounds



3 and **5** have been synthesized by this reaction, but yields were uncertain.[7] For **4** the use of the free base is reported to be precluded, as this method results in the formation of 1-(2-benzothiazolyl)benzotriazole.[8] However, using the sodium salt of the heterocycle, compound **4** is formed, though no yield is reported.[7,8]

A more general approach to the preparation of these compounds requiring only 2 mol of the heterocycle involves the reaction between its silylated derivative and thiophosgene. In this way we have synthesized not only **1, 3,** and **4** but also



1,1′-thiocarbonyldipyrazole (**6**), for which the known methods have been reported to fail.[7] In addition, a new reagent, 1,1′-thiocarbonyldi-1,2,4-triazole (**7**), was also made (Table I). In all cases, the yields are excellent (90–100%) and the purity of the crude product very high.[9] The silylated precursors were prepared from the heterocycle and hexamethyldisilazane (HMDS) according to the method of Birkofer.[10]

Although **3, 4,** and **6** are generally less reactive (compared to **1**) with compounds having labile hydrogen atoms (amines, alcohols, and thiols), the properties of the reagents (stability toward moisture) and the low solubility of the heterocycle formed by the reaction may in certain situations give these reagents advantages superior to **1**. In the case of **7,** we found

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