Preparation of Reissert Compounds Derived from the Thieno[3,2-*c*]pyridine, Thieno[2,3-*d*]pyridazine and the Thieno[2,3-*d*]pyrimidine Ring Systems

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Received March 22, 1985

The use of tributyltin cyanide, trimethylsilyl cyanide and potassium cyanide in the Reissert reaction is contrasted in the furo[3,2-*c*]pyridine, thieno[3,2-*c*]pyridine, thieno[2,3-*d*]pyridazine, and thieno[2,3-*d*]pyrimidine ring systems.

J. Heterocyclic Chem., **23**, 545 (1986).

Reissert chemistry has generated a rich methodology whose synthetic applications have yielded access to isoquinoline alkaloids, novel heterocycles, and unusual substitution patterns on quinoline and isoquinoline bases [1]. The extension of Reissert chemistry to heterocycles outside the quinoline and isoquinoline classes has served to further define the scope and utility of this reaction. The idiosyncratic chemical reactivity of these more exotic Reissert substrates has also challenged the development of new procedures to optimize this conversion. The use of trimethylsilyl cyanide in dichloromethane is slowly gaining favor as the reactive cyanide species in the Reissert reaction rather than the conventional use of potassium cyanide in the biphasic mixture of dichloromethane-water. Recently, application of trimethylsilyl cyanide in obtaining Reissert products from benzoxazole and benzothiazole has been reported [2]. Previous attempts to capture Reissert products from these five-membered nitrogen heterocycles under biphasic conditions employing potassium cyanide met with failure due to predominant ring opening reactions.

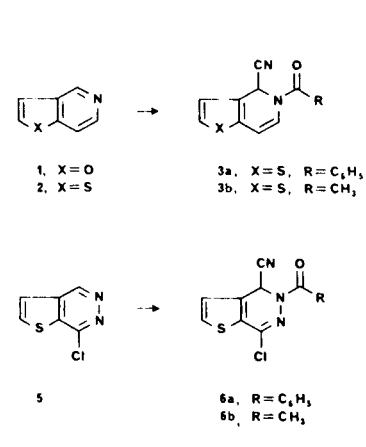
A report detailing the Reissert reactions of the thieno[2,3-*c*]pyridine heterocycle prompts us to communicate our experience with the isomeric thieno[3,2-*c*]pyridine ring, as well as the furo[3,2-*c*]pyridine, the thieno[3,4-*d*]pyridazine, and the thieno[2,3-*d*]pyrimidine ring systems [3]. We will also describe the first use of tributyltin cyanide as an effective cyanating agent in the Reissert reaction, and present a preliminary distinction between its reactivity and that of trimethylsilyl cyanide.

Results and Discussion.

Three different methods were explored to effect the Reissert reaction on the heterocycles reported herein: Method A represents the use of trimethylsilyl cyanide, together with the heterocycle and acyl halide in dichloromethane at room temperature; Method B uses a potassium cyanide source as the nucleophile in a biphasic mixture of dichloromethane and water; Method C is comparable to Method A, except that tributyltin cyanide is employed.

None of these approaches were successful in converting the furo[3,2-*c*]pyridine ring (1) into its Reissert products (Scheme 1). Methods A and C converted the starting material into multiple products none of which predominated or corresponded to the Reissert adduct. The reaction of **1** under conditions of Method B usually led to recovery of a minor amount of the hydrochloride salt of **1** in the aqueous layer, and numerous side products present in the organic phase. Trimethylsilyl cyanide (Method A) proved effective in obtaining Reissert products derived from the thieno[3,2-*c*]pyridine heterocycle **2**, with equivalent yields realized for either the benzoyl or acetyl chlorides. The lack of reactivity of this ring system under biphasic conditions is noteworthy (Table 2). This general pattern of reactivity is also observed in 7-chlorothieno-[2,3-*d*]pyridazine **5** where some product is obtained under the biphasic Reissert conditions, however, trimethylsilyl cyanide is the superior reagent to effect this conversion (Table 1).

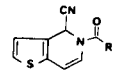
Scheme 1



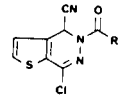
Neither methods A or B are applicable with the thieno-[2,3-*d*]pyrimidine ring (**9**). Although trimethylsilyl cyanide did render Reissert products as judged simply by tlc results, any attempts to work-up reaction mixtures obtained from Method A eventually led to decomposition of the

Table 1

Reissert Derivatives of the Thieno[3,2-*c*]pyridine and Thieno[2,3-*d*]pyridazine Heterocycles



	R	Method	MP °C	Yield (%)	Formula	Recrystallization Solvent	Analysis % Calcd. C	H	N	Found C	H	N
3a	C_6H_5	A	137-138	71.5	$C_{15}H_{10}N_2OS$	2-propanol	67.65,	3.79,	10.52	67.73,	3.84,	10.26
3b	CH_3	A	103	67	$C_{10}H_8N_2OS$	2-propanol-acetonitrile	58.81,	3.95,	13.92	58.65,	4.03,	13.64
3b	CH_3	B		0								

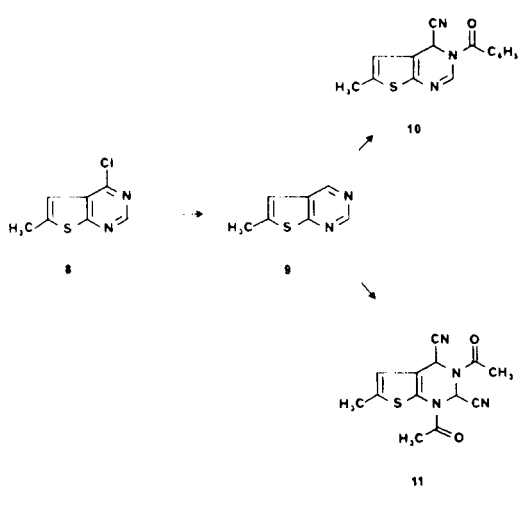


	R	Method	MP °C	Yield (%)	Formula	Recrystallization Solvent	Analysis % Calcd. C	H	N	Found C	H	N
6a	C_6H_5	A	175-177	87	$C_{14}H_8ClN_3OS$	2-propanol-acetonitrile	55.73,	2.67,	13.92	55.85,	2.72,	13.82
6b	CH_3	A	162-165	99	$C_9H_6ClN_3OS$	acetonitrile	45.10,	2.52,	17.53	45.28,	2.60,	17.92
6b	CH_3	B		14								

desired products. The work-up procedures in this case involved only one water wash of the reaction mixture and avoided the customary acid and base washes. Compound **9** is also unreactive under biphasic conditions using potassium cyanide in extended reaction times (10 days).

The use of a slight excess of tributyltin cyanide and acyl halide was effective in obtaining Reissert products derived from **9** (Scheme 2). The use of this reagent in the Reissert reaction has not previously been reported and may now extend this methodology to previous ring systems which have resisted either Methods A or B. Under identical reaction conditions, Method C yielded the mono-Reissert adduct with benzoyl chloride (**10**) and the di-Reissert product with acetyl chloride (**11**), when two equivalents each of tributyltin cyanide and the acyl chloride were used (Table 3). Downscaling to stoichiometic equivalents of **9**, acetyl chloride, and tributyltin cyanide, did not preclude formation of **11** but simply led to recovery of unreacted starting material with no evidence of the mono-Reissert product present. Additional applications of tributyltin cyanide, as well as alkylation and cycloaddition reactions concerning the new Reissert compounds reported herein, will be forthcoming.

Scheme 2

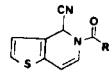


EXPERIMENTAL

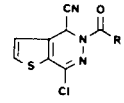
All ir spectra were recorded on a Nicolet MX-1 FT-IR spectrometer. The ^{1}H-nmr spectra were recorded on a Perkin-Elmer R-32 spectrometer, and the ^{13}C-nmr spectra were recorded on a Varian FT-80 spectrometer in 5 mm o.d. sample tubes in either deuteriochloroform, using 2% (v/v) tetramethylsilane as the internal reference, or perdeuteriodimethylsulfoxide. Melting points were determined using a Thomas-Hoover capillary apparatus and are uncorrected.

Table 2

IR, ^{1}H-NMR and ^{13}C-NMR Spectral Data of Compounds **3a-b**, and **6a-b**



Compound No.	IR, cm^{-1} (potassium bromide)	^{1}H-NMR (deuteriochloroform), δ (ppm)	^{13}C-NMR (deuteriochloroform), δ (ppm)
3a	3120-3060, 2960, 1655, 1610, 720-695	6.15 (1H, d, J = 8.0 Hz), 6.55 (1H, d, J = 8.0 Hz) 6.92 (1H, s), 7.26 (1H, d, J = 5.2 Hz), 7.50 (6H, m)	43.2 (d), 103.2 (d), 116.4 (s), 124.1 (s), 124.2 (d), 125.6 (d), 125.9 (d), 128.6 (d), 128.8 (d), 131.8 (d), 132.4 (s), 132.8 (s), 168.7 (s)
3b	3110, 1685, 1675, 1610, 1375, 1330, 1010, 895, 835, 705	2.30 (3H, s), 6.23 (1H, d, J = 8.0 Hz) 6.90 (1H, s), 6.97 (1H, d, J = 8.0 Hz) 7.21 (1H, d, J = 5.0 Hz), 7.50 (1H, J = 5.0 Hz)	21.3 (q), 42.0 (d), 116.7 (s) 123.3 (d), 123.7 (s), 125.7 (d), 132.7 (s), 169.3 (s)



6a	3110, 2970, 1670, 1600, 1495, 1545	7.25 (1H, s), 7.60 (6H, m) 814 (1H, d, J = 5.0 Hz)	42.5 (d), 115.5 (s), 126.7 (s), 126.9 (d), 127.9 (d), 129.9 (d), 131.9 (d), 131.9 (s), 132.2 (s), 134.5 (d), 135.1 (s), 169.1 (s)
6b	3100, 2960, 1685, 1560, 1535, 1375	2.40 (3H, s), 6.73 (1H, s), 7.19 (1H, d, J = 5.0 Hz), 7.67 (1H, d, J = 5.0 Hz)	21.0 (q), 41.6 (d), 115.3 (s), 126.6 (s), 126.9 (d), 131.4 (s), 134.0 (s), 134.2 (d), 171.1 (s)

Table 3

Derivatives of the Thieno[2,3-*d*]pyrimidine Heterocycle

Compound Number	Method	MP °C	Yield (%)	Formula	Recrystallization Solvent	Analysis Calcd. C	H	N	Found C	H	N
9 [a]	– – –	93-95	72	$C_7H_6N_2S$	[b]	55.98	4.03	18.65	55.82	4.08	18.45
10	C	152-155	94	$C_{15}H_{11}N_3OS$	EtOH-EtOAc (1:1)	64.04	3.94	14.94	64.09	4.04	15.15
11	C	190-193	63.5	$C_{13}H_{12}N_4O_2S$/ 0.15 H_2O	EtOH	53.65	4.26	19.25	53.43	4.12	19.12 [c]

[a] Compound **9** is 6-methylthieno[2,3-*d*]pyrimidine; compound **10** is 3-benzoyl-3,4-dihydro-6-methylthieno[2,3-*d*]pyrimidine-4-carbonitrile; compound **11** is 1,3-diacetyl-1,2,3,4-tetrahydro-6-methylthieno[2,3-*d*]-pyrimidine-2,4-dicarbonitrile. [b] Kugelrohred (bp 67-69°C, 0.4 mm). [c] Karl Fischer analysis indicates 0.05% water present.

General Procedure for the Synthesis of **3a-b** and **6a-b**.

Method A. 5-Acetyl-7-chloro-4,5-dihydrothieno[2,3-*d*]pyridazine-4-carbonitrile (**6b**).

A mixture of 1.0 g (6.0 mmoles) of 7-chlorothieno[2,3-*d*]pyridazine (**5**), 1.2 g (12 mmoles) trimethylsilyl cyanide and a catalytic amount of aluminum chloride in dichloromethane (70 ml) is treated dropwise with a solution of 1.0 g (12 mmoles) of acetyl chloride in dichloromethane (20 ml) at room temperature. After stirring for 1 hour, the mixture is washed with 3*N* sodium hydroxide (50 ml), 2*N* hydrochloric acid (50 ml), water (50 ml), and the organic phase is isolated, dried on magnesium sulfate, filtered, and the solvent removed on a rotary evaporator. Recrystallization of the collected solid from acetonitrile affords 1.4 g (99%) of **6b** as light yellow crystals.

Table 1 summarizes the physical data and Table 2 the spectral data of these compounds. The preparation of compounds **1**, **2**, and **5** is according to literature methods [4-6].

Method B.

A mixture of 0.6 g (3.6 mmoles) of 7-chlorothieno[2,3-*d*]pyridazine (**5**) in dichloromethane (35 ml) and 0.7 g (11 mmoles) of potassium cyanide in water (20 ml) is treated dropwise with a solution of 0.9 g (11 mmoles) of acetyl chloride in dichloromethane (15 ml) at room temperature. After stirring for 12 days the organic phase is isolated, washed with water (50 ml), 5% sodium carbonate (50 ml), and the organic phase dried on magnesium sulfate, filtered, and the solvent removed on a rotary

Table 4

IR, ^{1}H-NMR and ^{13}C-NMR Spectral Data of Compounds **9-11**

Compound No.	IR, cm^{-1} (potassium bromide)	^{1}H-NMR (deuteriochloroform), δ (ppm)	^{13}C-NMR (deuteriochloroform), δ (ppm)
9	3050, 1560, 1510, 1430-1375	2.62 (3H, d, J = 1.0 Hz), 6.94 (1H, q, J = 1.0 Hz) 8.93 (1H, s), 8.99 (1H, s)	16.5 (q), 117.1 (d), 132.0 (s) 142.7 (s), 149.8 (d), 152.5 (d), 168.6 (s)
10	3060, 2920, 1680, 1585, 720	2.49 (3H, s), 6.26 (1H, s), 6.65 (1H, m), 7.58 (6H, m)	15.3 (q), 42.4 (d), 115.0 (s) 116.3 (s), 122.1 (d), 128.9(s) 129.4 (s), 131.8 (d), 132.6 (s) 137.9 (s), 140.3 (s), 143.0 (s), 169.6 (s)
11	1685, 1570, 1395	2.40 (3H, s), 2.43 (6H, s), 6.54 (1H, br s), 6.82 (1H, m), 7.60 (1H, br s)	14.4 (q), 21.1 (q), 21.4 (q), 40.0 (d), 53.0 (d), 113.5 (s), 115.0 (s), 115.6 (s), 119.8 (d), 130.9 (s), 135.6 (s), 166.2 (s), 169.1 (s)

evaporator affording a yellow-orange solid. Flash chromatography (chloroform) of this solid yielded 0.12 g (14%) of product and 0.40 g of **5**.

Method C. 3-Benzoyl-3,4-dihydro-6-methylthieno[2,3-*d*]pyrimidine-4-carbonitrile (**10**).

A mixture of 1.0 g (6.7 mmoles) of 6-methylthieno[2,3-*d*]pyrimidine (**9**), 4.2 g (13.3 mmoles) of tributyltin cyanide, and a catalytic amount of aluminum chloride in dichloromethane (40 ml) is treated dropwise with a solution of 1.9 g (13.3 mmoles) of benzoyl chloride in dichloromethane (15 ml) at room temperature. After stirring for 30 minutes, the yellow mixture is washed with 5% sodium carbonate (50 ml), 2*N* hydrochloric acid (50 ml), water (50 ml), and the organic phase is isolated, dried over magnesium sulfate, filtered, and the solvent removed on a rotary evaporator affording a yellow solid. Recrystallization from ethanol-ethyl acetate (1:1) yielded 1.8 g (94%) of a solid which contained a miniscule amount of the di-Reissert product as a contaminant. Flash chromatography (chloroform) provided 1.2 g (68%) of pure **10**. The reaction time for synthesis of **11** is 80 hours.

Table 3 summarizes the physical data and Table 4 the spectral data of compounds **9-11**.

6-methylthieno[2,3-*d*]pyrimidine (**9**).

A mixture of 1.0 (5.4 mmoles) of 4-chloro-6-methylthieno[2,3-*d*]pyrimidine (**8**) [7] and 3 g of zinc in ethanol at room temperature is slowly treated dropwise with glacial acetic acid and gently warmed to 80° for 24 hours. The solvent is removed on the rotary evaporator, the collected residue dissolved in dichloromethane (80 ml) and washed with 5% sodium carbonate. The organic phase is isolated, dried on magnesium sulfate, filtered, and the solvent removed on the rotary evaporator affording a solid which is Kugelrohered (120°, 0.4 mm) to provide 0.6 g (72%) of white crystals.

REFERENCES AND NOTES

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