$CDCl_3$) δ 8.45 (br s, 3 H, NH_3^+), 7.22 (AA'BB' doublet, 2 H, J = 8.8 Hz, H-2 and H-6 of ring), 6.90 (AA'BB' doublet, 2 H, J = 8.8 Hz, H-3 and H-5) 5.54 (s, 1 H, olefinic H), 5.43 (s, 1 H, olefinic H), 3.99 (s, 2 H, CH_2N), 0.97 (s, 9 H, *t*-Bu), 0.19 (s, 6 H, CH_3); MS (CI/CH_4), m/z 264 (100, MH^+), 248 (20, M - CH_3), 206 (10, M - C_4H_9). The product was further characterized by deprotection to give **1i**.

β-(4-Fluorophenyl)-β-methyleneethanamine 4-methylbenzenesulfonate salt (1h) was prepared by the procedure used for **1b** and isolated initially as the HCl salt in 56% yield according to method B. The salt, although spectroscopically pure, proved difficult to recrystallize and was converted to the free base and bulb-to-bulb distilled (90-100 °C, 2.5 torr) to provide a colorless oil in 49% yield based on **2**. Addition of 1.0 equiv of 1.0 M *p*-TsOH in EtOH to an ether solution of the free base gave a tosylate salt which was recrystallized from CH_3CN to give colorless needles: mp 172-173 °C; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 8.10 (br s, 3 H, NH_3^+), 7.57 (dd, 2 H, J_{HH} = 9.0 Hz, J_{HF} = 5.4 Hz, H-2 and H-6 of ring), 7.48 (d, 2 H, J = 7.8 Hz, H-2' and H-6' of tosylate), 7.25 (dd, 2 H, J_{HH} = 9.0 Hz, J_{HF} = 8.8 Hz, H-3 and H-4), 7.12 (d, 2 H, J = 7.8 Hz, H-3' and H-4'), 5.65 (s, 1 H, olefinic H), 5.35 (s, 1 H, olefinic H), 3.94 (s, 2 H, CH_2N), 2.29 (s, 3 H, CH_3); MS (CI/CH_4), m/z 173 (70, *p*-$TsOH_2^+$), 3.94 (s, 2 H, CH_2N), 2.29 (s, 3 H, CH_3); MS (CI/CH_4), m/z 173 (70, *p*-$TsOH_2^+$) 152 (100, MH^+), 135 (50, MH^+ - NH_3), 132 (40, MH^+ - HF), 123 (20, MH^+ - CH_2=NH).

Anal. Calcd for $C_9H_{10}FN \cdot C_7H_8O_3S$: C, 59.43; H, 5.61; N, 4.33. Found: C, 59.28; H, 5.77; N, 4.28.

β-(4-Hydroxyphenyl)-β-methyleneethanamine Hydrochloride (1i). To a mixture of 0.80 g (2.7 mmol) of **1g**, 10 mL of water, and 4 mL of THF was added 1.50 g (25.8 mmol) of anhydrous KF. The mixture was stirred at ambient temperature for 16 h, then was saturated with NaCl, and diluted with 25 mL of THF. The layers were separated and the aqueous layer was extracted with more THF (2 × 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated to dryness. The residue was taken up in CH_3OH and treated with methanolic HCl and then concentrated to dryness. The residue was recrystallized from 2-propanol to afford 0.31 g (62%) of dark crystals: mp 172 °C (lit.[1e] mp 175 °C); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 9.70 (br s, 1 H, OH), 8.30 (br s, 3 H, NH_3^+), 7.34 (d, 2 H, J = 9 Hz, H-2 and H-6 of benzene ring), 6.97 (d, 2 H, J = 9 Hz, H-3 and H-5), 5.51 (s, 1 H, olefinic H), 5.21 (s, 1 H, olefinic H), 3.85 (br s, 2 H, CH_2N); MS (EI/70 eV), m/z 149 (100, M^+), 132 (50, M - NH_3), 120 (80), 119 (60, M - CH_2NH_2), 91 (50).

Anal. Calcd for $C_9H_{11}NO \cdot HCl$: C, 58.22; H, 6.52; N, 7.54. Found: C, 58.40; H, 6.44; N, 7.54.

β-(3,4-Dichlorophenyl)-β-methyleneethanamine (1j) was prepared by the procedure used for **1b**, isolated by method A, and subsequently converted to the HCl salt, mp 173-174 °C, after recrystallization from CH_3CN: ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 8.48 (br s, 3 H, NH_3^+), 7.83 (d, 1 H, $J_{2,6}$ = 1.8 Hz, H-2 of ring), 7.68 (d, 1 H, $J_{5,6}$ = 9.0 Hz, H-5), 7.54 (dd, 1 H, $J_{6,5}$ = 9.0 Hz, $J_{6,2}$ = 1.8 Hz, H-6), 5.79 (s, 1 H, olefinic H), 5.53 (s, 1 H, olefinic H), 3.93 (s, 2 H, CH_2N); MS (CI/CH_4), m/z 202 (100, MH^+), 185 (40, MH^+ - NH_3).

Anal. Calcd for $C_9H_9Cl_2N \cdot HCl$: C, 45.32; H, 4.22; N, 5.87. Found: C, 45.50; H, 4.27; N, 6.04.

β-Methylene-β-(2-benzo[*b*]thienyl)ethanamine hydrochloride (1k) was prepared by the procedure used for **1a** and isolated by method B: mp 231 °C; ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 8.35 (br s, 3 H, NH_3^+), 7.95 (m, 1 H, benzene H), 7.82 (m, 1 H, benzene H), 7.63 (s, 1 H, H-3 of thiophene), 7.41 (m, 1 H, benzene H), 7.38 (m, 1 H, benzene H), 5.75 (s, 1 H, olefinic H), 5.50 (s, 1 H, olefinic H), 4.02 (s, 2 H, CH_2N); MS (CI/CH_4), m/z 190 (100, MH^+), 173 (20, MH^+ - NH_3), 149 (10, M - CH_2NH_2).

Anal. Calcd for $C_{11}H_{11}NS \cdot HCl$: C, 58.52; H, 5.36; N, 6.20. Found: C, 58.75; H, 5.38; N, 6.19.

β-Methylenehexanamine hydrochloride (1l) was prepared by the procedure used for **1b** and isolated by method B: mp 170.5-172.5 °C (softens at 103-105 °C); ^1H NMR (300 MHz, $(CD_3)_2SO$) δ 8.28 (br s, 3 H, NH_3^+), 5.09 (s, 1 H, olefinic H), 4.99 (s, 1 H, olefinic H), 3.35 (s, 2 H, CH_2N), 2.06 (t, 2 H, J = 7.3 Hz, allylic H), 1.2-1.5 (m, 4 H, remaining methylene H), 0.89 (t, 3 H, J = 7.1 Hz, CH_3); MS (EI/70 eV), m/z 114 (7, M + H), 113 (2, M^+), 96 (15, M - NH_3), 84 (10, M - CH_2=CHC(=CH_2)CH_2NH_3), 81 (30), 70 (80, M - CH_2C(=CH_2)CH_2NH_2), 56 (100, M - C_4H_9).

Anal. Calcd for $C_7H_{15}N \cdot HCl$: C, 56.18; H, 10.78; N, 9.36. Found: C, 56.01; H, 10.59; N, 9.35.

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Registry No. **1a**·HCl, 99605-88-6; **1b**, 28144-67-4; **1c**·HCl, 106191-57-5; **1d**, 106191-58-6; **1e**, 106191-59-7; **1f**, 106191-60-0; **1g**, 106191-61-1; **1h**, 106191-62-2; **1h**·HCl, 106191-67-7; **1h**·4-$MeC_6H_4SO_3H$, 106191-63-3; **1i**·HCl, 98420-46-3; **1j**, 106191-64-4; **1j**·HCl, 106191-68-8; **1k**·HCl, 106191-65-5; **1l**·HCl, 106191-66-6; **2**, 106191-56-4; H_2C=C(Cl)CH_2NH_2 ., 38729-96-3; PhBr, 108-86-1; 4-MeC_6H_4Br, 106-38-7; 4-$MeOC_6H_4Br$, 104-92-7; 3-$MeOC_6H_4Br$, 2398-37-0; 3,4-$(MeO)_2C_6H_3Br$, 2859-78-1; 4-*t*-$BuMe_2SiOC_6H_4Br$, 67963-68-2; 4-FC_6H_4Br, 460-00-4; 3,4-$Cl_2C_6H_3Br$, 18282-59-2; C_4H_9Br, 109-65-9; $ClMe_2Si(CH_2)_2SiMe_2Cl$, 13528-93-3; thiophene, 110-02-1; 2-bromo-benzo[*b*]thiophene, 5394-13-8.

Inorganic-Solid-Supported Potassium Thiocyanate: Study of Reagent Preparation and a Convenient Synthesis of *tert*-Alkyl Thiocyanates

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The development of inorganic reagents adsorbed on high surface area supports has received much attention during the last decade and several common metal salts have thus been simply activated to produce valuable reagents for the organic synthetic chemist.[1,2] Our previous studies have shown that considerable improvement in reagent reactivity and selectivity may be gained by careful selection of support material and control of salt dispersion by optimization of loading and drying conditions.[3-5] The activation of KCN in the presence of alumina has been reported[6] and we recently developed highly reactive KCN-Al_2O_3 reagents,[7] enabling facile cyanation, with the use of infrared spectroscopy to study the metal cyanide-support interaction.[8]

Our attention was turned toward thiocyanation since although the reaction of metal thiocyanates with alkyl halides represents a valuable synthesis of organic thiocyanates, important intermediates for heterocyclic syntheses,[9] the literature contained only two short communications reporting silica gel supported potassium thiocyanate reagents for syntheses of some primary alkyl thiocyanates[10] and thiiranes.[11] We now report the use of infrared spectroscopy to enable straightforward monitoring of reagent preparation and show that some highly reactive supported reagents can be prepared. These allow some hitherto troublesome syntheses of *tert*-alkyl thiocyanates to be performed in moderate yield but with a high degree of selectivity and convenience.

Results and Discussion

Among the inorganic supports which were previously investigated for KSCN, the effectiveness was reported to

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Table I. Thiocyanation of Primary and Secondary Halides with KSCN-Support

run	substrate[a]	support	loading[b]	time, h	convn,[c] %	selectivity,[c] % SCN	NCS
1	$PhCH_2Br$	none		1; 5	5; 25	100	
2		SiO_2	2	3	62	100	
3			3	1	96	100	
4			10	1; 3	69; 96	100	
5		Al_2O_3	0.9	0.5; 3	45; 23	100	
6			2	0.5; 3	92; 77	100	
7			10	0.5; 3	32; 68	100	
8	$PhCH_2Cl$	none[d]		2; 7	55; 91	100	
9		SiO_2	2	7	100	100	
10			3	2; 7	77; 100	100	
11			10	7	66	100	
12	*n*-BuBr	SiO_2	3	6[e]	100	100	
13			10	6[e]	72	100	
14	$PhCH(Br)CH_3$	SiO_2	3	3	97	91	9
15		Al_2O_3	2	20[f]	96	94	6
16			0.9	2.5	87	93	7
17		CaF_2	0.5	20	100	95	5

[a] 0.5 mmol in 5.0 mL of cyclohexane with KSCN-support (1.25 mmol of KSCN) shaken at 50 °C, unless otherwise indicated. [b] mmol KSCN/g of support, dried at 50 °C (2.66 kPa) for several hours. [c] Determined by GLC using a 3% OV-17 on Chromosorb W column. [d] Homogeneous reaction in MeCN. [e] 7.5 molar equiv of KSCN, reaction at 80 °C. [f] At room temperature without solvent.

decrease as $SiO_2 > Al_2O_3 >$ MS 5A > MS 13X > Kieselguhr, and it was noted that reaction without solvent was most effective.[10] However, although the surface area of these supports must decrease quite markedly across the series, the salt impregnation was kept at 10 mmol/g of support, a loading which would be well above the theoretical "monolayer coverage" (ca. 5 "molecule"/nm^2), which we observed to give near optimum salt dispersion for supported KCN.[7,8] Infrared spectra in the 2100–1920 cm^{-1} region of KSCN–silica and KSCN–alumina prepared at 10 mmol/g (ca. 15 and 50 "molecules"/nm^2, respectively) are shown in Figure 1. The clear strong band due to the asymmetric SCN^- stretching mode appears at 2050 cm^{-1} and comparison with the parent salt shows that it occurs at the same frequency, although the supported salt does show a pronounced shoulder at ca. 2075–70 cm^{-1}, most notable on the higher surface area silica. Comparison with the spectra of reagents loaded at 5–10 "molecules"/nm^2 (e.g., 3 mmol/g KSCN–silica and 2 mmol/g KSCN–alumina, Figure 1) shows the ν (SCN) band totally shifted to 2075–70 cm^{-1}, suggesting that this absorption is due to well-dispersed KSCN, which has significantly less ion pairing than the parent salt. The spectra of the 10 mmol/g reagents thus suggest that the KSCN is "overloaded", in that dispersion is rather poor and a significant amount of the salt is present in large clusters.

The chemical reactivities of the variously loaded reagents were compared for the thiocyanation of benzyl halides. Table I gives the percent conversion to $PhCH_2SCN$, the values (by GLC after release of adsorbed organics from the supported reagents with the addition of a small amount of water to the reaction mixture) clearly show that greater reactivity may be obtained with lower KSCN loadings. It was noted that surface adsorption of both reactant and product organics from solution was much greater for the lower loaded reagents. Thus considering that reaction will occur at the reagent surface, it is also understandable why the highly loaded 10 mmol/g KSCN–silica was previously reported to give best results when reactants were impregnated and the reagents used without solvent.[10] The near optimum loadings for silica and alumina appear to be 3 and 2 mmol/g, respectively (5–10 molecules/nm^2), the

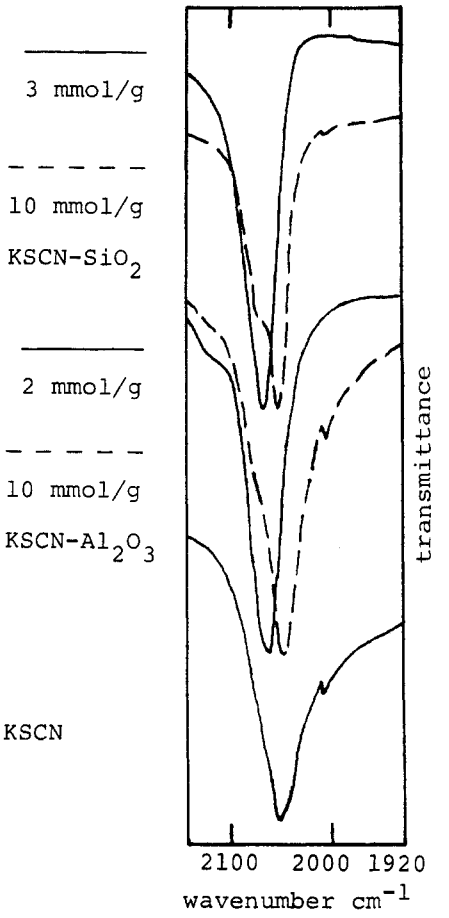

Figure 1. Infrared spectra of KSCN and KSCN–support.

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Table II. Thiocyanation of Allyl Halides with KSCN-Support

run	substrate[a]	support	loading[b]	time, h	convn,[c] %	selectivity,[d] % SCN	selectivity,[d] % NCS
1	$PhCH{=}CHCH_2Br$	Al_2O_3	2	4	59[e]		
2	$PhCH{=}CHCH_2Cl$	SiO_2	2	2[f]	86	73	27
3			3	2[f]	79	85	15
4			3	2	98	70	30
5			3	20	98	28	72
6			10	2[f]	64	91	9
7			10	3	97	78	22
8			10	20	98	57	43
9		Al_2O_3	2	2	98	79	21
10			2	20	98	53	47
11			10	3	93	75	25
12			10	20	97	70	30
13		CaF_2	0.5	15	97	71	29
14			0.5	3	98	75	25
15			1.5	15	98	72	28
16		Florisil	2	2	98	65	35
17			2	20	99	19	81

[a] 0.5 mmol in 5.0 mL of cyclohexane with KSCN-support (1.25 mmol of KSCN) shaken at 50 °C, unless otherwise indicated. [b] mmol KSCN/g of support, dried at 50 °C (2.66 kPa). [c] Isolated yields from solvent evaporation of collected reaction supernatant and ether washes of the reagent. [d] Determined by ^1H NMR (GLC determination caused isomerization of these compounds). [e] Isolated in 94% purity by ether washing of the reagent, after previously filtering and washing the reagent with hexane to separate isothiocyanate. [f] Without solvent.

reactivity of the former being greater than that of a homogeneous KSCN–MeCN mixture. Table I also shows the facile thiocyanation of *n*-butyl bromide and 1-bromo-1-phenylethane with the KSCN–support reagents.

It may be noted that KSCN, unlike KCN,[7,8] is highly effective for substitution on both silica and alumina although the latter gave a decreased yield of $PhCH_2SCN$ over a longer reaction time as dibenzyl disulfide byproduct was formed.[12] The activation of KSCN by impregnating it on these high surface area inorganic supports did not appear to be specific and reagents of similar activity were prepared by using three other supports of quite different nature. Highly pure calcium fluoride (10–20 m^2/g), recently reported as an activating support for KF,[13] Florisil (100–200 mesh), and K10 montmorillonite clay (220–270 m^2/g) all gave active reagents, as long as the loadings were suitably adjusted. Infrared monitoring of CaF_2, Florisil, and K10 reagents showed the ν(SCN) band at 2075–70 cm^{-1} when loaded at 0.5,[14] 2, and 3 mmol/g, respectively.

The reaction of 2.5 molar equiv of the optimized KSCN–support reagents with cinnamyl halides gave rapid thiocyanation in good yield as shown in Table II, although the isomerization to isothiocyanate was found to be promoted by the lower loaded silica and alumina supported reagents with time. A similar effect has been reported for polymer-supported KSCN.[15,16] Reaction was appreciably slower with the 10 mmol/g reagents (even for reaction without solvent), but the selectivity was retained over a long reaction time, presumably because very little support surface was then available to catalyze the isomerization. The CaF_2-supported reagent gave rapid thiocyanation and did not promote the isomerization, giving cinnamyl thiocyanate in 75% yield.

The reaction of *tert*-alkyl halides with KSCN does not generally represent a useful synthesis of the corresponding thiocyanates, due to typically low conversions[17] and a general increase in the preference for the isothiocyanates, rationalized for the S_N1 reactions on the basis of the hard and soft acids and bases (HSAB) principle.[18] Table III shows the conversion and isomer selectivities obtained for substitution at the tertiary carbon centers of some *tert*-alkyl halides and an α-bromo ester with a variety of thiocyanate reagents under different conditions. With the supported KSCN reagents the α-bromo ester gave clean S_N2 reaction to selectively afford the thiocyanate whereas the *tert*-alkyl halides were converted in good yield, giving variable amounts of both isomers by S_N1 reaction. All of the supported KSCN reagents gave much improved conversion compared to heterogeneous powdered KSCN or homogeneous KSCN–MeCN and KSCN–DMF[17] mixtures. The isomer selectivity values of S/N for the *tert*-alkyl substitutions ranged between 2 and 9 with the various supported reagents, a similar range to that once reported by Taft and Cannell[19] for the product ratios in the reaction of SCN^- with certain tertiary carbonium ion precursors. However, the S/N selectivities were appreciably lower with the KSCN–MeCN or KSCN–DMF[17] reagent mixtures.

For the *tert*-alkyl substitution it may be noted that the highest yield of thiocyanate, together with a high S/N isomer ratio, is obtained with the low loaded KSCN–alumina reagents used with solvent. One other interesting point noted was the fact that the isothiocyanate was almost exclusively present in solution whereas the thiocyanate was often adsorbed on the reagent surface, by as much as 80% based on final yield in the case of the low loaded KSCN–silica. These observations led us to attempt these *tert*-alkyl thiocyanation reactions using a column of the supported KSCN reagents, in an effort to give a clean separation of the isomers, which were not easily separated by column chromatography on silica gel or alumina due to much product decomposition. The KSCN–alumina reagent alone failed to give good separation of the isomers but it did improve the selectivity and final yield when it was packed above KSCN–silica. Thus an effective column packing was found to consist of KSCN–alumina above KSCN–silica (2

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Table III. Thiocyanation at Tertiary Carbon Centers of *tert*-Alkyl Halides and an α-Bromo Ester with KSCN-Support

run	substrate[a]	support	loading[b]	time, h	convn,[c] %	selectivity,[d] % SCN	selectivity,[d] % NCS
1	*t*-BuBr	none		24	6	83	17
2				3[e]	6	33	67
3		SiO_2	3	3	96	66	34
4			10	3	59	64	36
5		Al_2O_3	0.9	3	80	90	10
6			2	2	85	79	21
7			2	2[f]	65	78	22
8			2	20[g]	75	80	20
9			10	2	68	76	24
10			10	20[f,g]	72	79	21
11		CaF_2	0.5	20[f,g]	74	77	23
12		K10	3	2	64	80	20
13	*t*-AmBr	none		3[e]	10	40	60
14		SiO_2	3	3	100	69	31
15			10	5	90	61	39
16		Al_2O_3	0.9	2.5	53	87	13
17			2	2	66	88	12
18			2	20[f,g]	77	64	36
19		CaF_2	0.5	20[g]	72	88	12
20		Florisil	2	3	67	81	19
21	1-AdBr	SiO_2	3	24	54	58	42
22		Al_2O_3	2	24	55; 80[h]	78	22
23		Florisil	2	24	41	74	26
24		K10	3	24	48	80	20
25	$(Me)_2CBrCO_2Et$	SiO_2	3	24	50; 99[h]	100	
26			10	24	20	100	

[a] 0.5 mmol in 5.0 mL of cyclohexane with KSCN–support (1.25 mmol of KSCN) shaken at 50 °C, unless otherwise indicated. [b] mmol KSCN/g of support, dried at 50 °C (2.66 kPa). [c] Sum of thiocyanate and isothiocyanate yield determined by GLC. [d] By GLC (3% OV-17 or 10% PEG 20M on Chromosorb W) using tetradecane internal standard. [e] Homogeneous reaction in MeCN. [f] Without solvent. [g] At room temperature. [h] At reflux.

Table IV. Thiocyanation Using a Column of KSCN–Support

substrate	column composition[a]	isolated yield of SCN,[b] %	purity,[c] %
t-Bu	A	13	96
	S	36	99
	F	5	98
	A + Al_2O_3	1	99
	A + Florisil	33	99
	A + S	53	97
	A + S	45[d]	96
t-AmBr	A + S	41[d]	95

[a] A = KSCN–alumina, 2 mmol/g; S = KSCN–silica, 3 mmol/g; F = KSCN–Florisil, 2 mmol/g. Reactions were performed with a jacketed glass column (30-cm long, 1-cm diameter) and the columns using two reagents were packed with the KSCN–alumina at the top. [b] *tert*-Butyl thiocyanate decomposes near its boiling point (140 °C) and has a high vapor pressure making it difficult to readily remove solvent. Values are estimated by GLC (3% OV-17) before concentration of the recovered solutions. [c] Determined by GLC, major impurity is isothiocyanate. [d] Preparative scale using 30-cm long, 2-cm diameter glass column.

and 3 mmol/g, respectively) with a small amount of activated charcoal at the bottom. Some isolated yields of *tert*-butyl and *tert*-amyl thiocyanates afforded using column reactions are given in Table IV. Although the pure thiocyanates may be obtained by careful removal of solvent, this would often be unnecessary when they are required as intermediates for synthesis.

We have shown that KSCN is activated for nucleophilic substitution on a variety of inorganic support materials, including both silica and alumina, and that these reagents may be used for a convenient synthesis of *tert*-alkyl thiocyanates with a fixed-bed type reactor of optimally loaded reagents. It would seem that the increase in KSCN activity is largely due to efficient salt dispersion over the high surface area of the supports, resulting in reduced ion pairing at optimum coverages as observed by IR analysis. However, the ability of solid supports to stabilize relatively unsolvated carbonium ions[20] may also be of value in aiding the S_N1 thiocyanations.

Experimental Section

Infrared spectra were obtained on a Nicolet 5DX FT IR spectrometer from KBr disks of the KSCN–supports (ca. 20:1 wt/wt). ^1H and ^{13}C NMR were run on a JEOL JNM-GX270 FT NMR spectrometer operating at 270.05 and 67.8 MHz, respectively. Analysis by GLC was conducted with a Shimadzu GC-7A instrument connected to a C-R2AX data analyzer, using columns as indicated in the tables. The silica used was Merck 60 (70–230 mesh for column chromatography), alumina was Merck 90 (grade 1, neutral for column chromatography), Florisil was from Floridin Co. (100–200 mesh), and CaF_2 was from Morita Kagaku Kogyo Co., Ltd. Solvents were routinely dried before use but all other chemicals were commercial materials used without further treatment. The supported reagents were prepared by thorough mixing of a solution of KSCN in water (ca. 1 M) with the measured amount of support followed by slow evaporation of the mixture on a rotary evaporator. Final drying of the resulting white solids was generally achieved at 50 °C (2.66 kPa)[21] and all were free flowing powders except the 10 mmol/g loadings which required light grinding. Reactions were performed in Teflon-coated screw-capped test tubes, shaken in a thermostatted water bath with a Tokyo Rikakikai Co. minivapor apparatus.

Reactions for Comparison of Reagent Activities. (a) The substitutions of primary, secondary, and tertiary halides, using the various KSCN reagents, were monitored by GLC analysis. In a typical reaction, *tert*-amyl bromide (63 μL, 0.5 mmol) was added to a mixture of the supported thiocyanate (e.g., 0.78 g of the 2 mmol/g KSCN–alumina, equivalent to 1.25 mmol of KSCN) and 5.0 mL of cyclohexane containing tetradecane as an internal standard (300 μL added to 100 mL solvent). The supernatant was intermittently sampled and before the final measurement

(20) Kramer, G. M.; McVicker, G. B. *Acc. Chem. Res.* **1986**, *19*, 78.
(21) The activity of KSCN–alumina was rather independent of drying conditions, the reaction with benzyl chloride being promoted to within excess of 80% with reagents containing molar ratios of water/salt in the range of 0.2–3.0. Increasing the drying of KSCN–alumina [115 °C (13.3 Pa)] increased thiocyanation and decreased byproduct formation by ca. 10% and 5%, respectively.

ca. 1 mL of H_2O was added and thoroughly mixed with the reaction mixture for ca. 1 min. The reaction products and percent conversion were determined by comparison with authentic materials and mass spectrometry. (b) The cinnamyl halide substitutions were analyzed by ^1H NMR of the recovered organic material. Cinnamyl chloride (76 mg, 0.5 mmol) was shaken with the KSCN–support (2.5 molar equiv of KSCN) in 5.0 mL of cyclohexane, or without solvent as stated, at the indicated temperature. The reaction products were isolated by filtration and ether washing of the solid reagents, followed by evaporation of the combined fractions. ^1H NMR ($CDCl_3$) δ 3.73 (d, J = 7.5 Hz, CH_2SCN), 4.27 (d, J = 5.6 Hz, CH_2NCS).

Ethyl 2-Methyl-2-thiocyanatopropanoate[22] **(1).** A preparative scale synthesis involved stirring ethyl 2-bromo-2-methylpropanoate (0.39 g, 2 mmol) with KSCN–silica (2.18 g, 5 mmol of KSCN) in 15 mL of cyclohexane at gentle reflux for 24 h. The warm mixture was filtered through $MgSO_4$ and charcoal and the solid reagent further washed with diethyl ether. Evaporation of the combined filtrates afforded 1: yield 91%; bp 213–215 °C; ^{13}C NMR ($CDCl_3$) δ 171.1 (s, CO), 110.7 (s, SCN), 62.8 (t, CH_2), 55.1 (s, $(CH_3)_2C$), 26.7 (q, $(CH_3)_2C$), 13.9 (q, CH_3CH_2); ^1H NMR ($CDCl_3$) δ 1.33 (t, 3 H), 1.77 (s, 6 H), 4.27 (q, 2 H); IR (neat) 2150 (s, SCN), 1720 (C=O) cm^{-1}.

Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.40; N, 8.09; S, 18.51. Found: C, 48.04; H, 6.38; N, 8.22; S, 18.59.

1-Thiocyanatoadamantane[23] **(2)** was prepared by stirring 1-bromoadamantane (1.08 g, 5 mmol) with KSCN–alumina (7.5 g, 12.5 mmol of KSCN) in 15 mL of cyclohexane at gentle reflux for 24 h. The complete reaction mixture was poured into a column slurry packed (hexane) with 16 g of KSCN–silica (3 mmol/g)[24] and then products were eluted with hexane, followed by hexane/ether (50/50) and finally ether. The hexane fraction contained isothiocyanate (20%) plus impurities, while **2** was isolated from the ether-containing fractions[25] as a white crystalline solid after removal of solvent under vacuum: yield 38%; mp 65–66 °C [lit.[23] mp 66–67 °C]; ^{13}C NMR ($CDCl_3$) δ 110.9 (s, SCN), 43.7 (t, CH_2), 35.5 (t, CH_2), 30.3 (d, CH); ^1H NMR ($CDCl_3$) δ 1.72 (6 H), 2.07 (6 H), 2.16 (3 H); IR (KBr) 2145 (s, SCN) cm^{-1}.

***tert*-Butyl Thiocyanate**[26] **(3).** Preparative scale synthesis using a column involved passing *tert*-butyl bromide (4.0 mL, 35 mmol) down a water-jacketed column (2-cm diameter, 30-cm long) slurry packed (hexane) from bottom upward with activated charcoal (1.5 g), KSCN–silica (28 g, 65 mmol of KSCN), and KSCN–alumina (40 g, 67 mmol of KSCN). Elution with hexane was sufficiently slow to allow reaction on the column for 2–3 h while at 50 °C. The eluant was collected in fractions and monitored by GLC (isothiocyanate eluted first). Finally, after isothiocyanate had been eluted, the column was brought to room temperature and a hexane/ether (40/60) mixture was used to elute the remaining thiocyanate. For isolation of the pure thiocyanate the solvent was removed from the suitable combination of collected fractions by fractional distillation (under vacuum with a N_2 bleed to reduce product decomposition) to give **3**; yield 35%; bp 40 °C (1.33 kPa) [lit.[26] bp 39–40 °C (1.33 kPa)]; ^{13}C NMR ($CDCl_3$) δ 111.7 (s, SCN), 51.9 (s, $C(CH_3)_3$), 30.9 (q, CH_3); IR (neat) 2130 (s, SCN) cm^{-1}.

***tert*-Amyl thiocyanate**[27] was prepared similarly: yield 33%; bp 59–60 °C (1.33 kPa) [lit.[27] bp 57–60 °C (1.33 kPa)]; ^{13}C NMR ($CDCl_3$) δ 111.8 (s, SCN), 56.3 (s, $C(CH_3)_2CH_2$), 35.5 (t, CH_2), 28.2 (q, $2CH_3$), 9.2 (q, CH_3CH_2); IR (neat) 2130 (s, SCN) cm^{-1}.

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Registry No. 1, 106162-82-7; 2, 39825-84-8; 3, 37985-18-5; $(Me)_2CBrCO_2Et$, 600-00-0; KSCN, 333-20-0; $BrC(CH_3)_3$, 507-19-7; $(CH_3)_2C(Br)CH_2CH_3$, 507-36-8; $(CH_3)_2C(CH_2CH_3)SCN$, 84356-30-9; $PhCH_2Br$, 100-39-0; $PhCH_2Cl$, 100-44-7; $CH_3(CH_2)_3Br$, 109-65-9; $PhCH(Br)CH_3$, 585-71-7; CaF_2, 7789-75-5; $PhCH_2SCN$, 3012-37-1; $CH_3(CH_2)_3SCN$, 628-83-1; $PhCH(SCN)CH_3$, 106162-83-8; $PhCH(NCS)CH_3$, 4478-92-6; $PhCH{=}CHCH_2Cl$, 2687-12-9; $PhCH{=}CHCH_2SCN$, 74394-96-0; $PhCH{=}CHCH_2NCS$, 65788-85-4; $(CH_3)_3CNCS$, 590-42-1; $CH_3CH_2C(CH_3)_2NCS$, 597-97-7; silica, 7631-86-9; 1-bromoadamantane, 768-90-1; alumina, 1344-28-1; Florisil, 1343-88-0; montmorillonite k 10, 1318-93-0; 1-adamantyl isothiocyanate, 4411-26-1.

(22) The corresponding methyl ester has been prepared by using KSCN in aqueous MeOH, 10 h reflux, 75%; Gagnon, P. E.; Boivin, J. L.; Brown, G. M. *Can. J. Chem.* **1959**, *37*, 1597.

(23) Previously prepared from sodium 1-adamantyl sulfide and tosyl cyanide (71% yield) or cyanogen chloride (36% yield) (Stetter, H.; Krause, M.; Last, W. D. *Chem. Ber.* **1969**, *102*, 3357) and also be reduction of 1-adamantanesulfinyl cyanide with triphenylphosphine (87% yield) (Boerma-Markerink, A.; Jagt, J. C.; Meyer, H.; Wildeman, J.; van Leusen, A. M. *Synth. Commun.* **1975**, *5*, 147).

(24) This reagent showed selective adsorption of **2** over the isothiocyanate for reactions in cyclohexane (Table III).

(25) Unreacted bromide is finally eluted, thus the eluant should be collected in fractions to prevent contamination of the desired product.

(26) Previous synthesis: reaction of *tert*-butyl chloride in aqueous NH_4SCN with $ZnCl_2$ (yield; 78/22% mixture of SCN/NCS). Schmidt, E.; Striewsky, W.; Seefelder, M.; Hitzler, F. *Ann.* **1950**, *568*, 192.

(27) Previous synthesis: reaction of *tert*-amyl sulfide with cyanogen chloride in ether, 10 °C, 3 days, yield 30%: Luskin, L. S.; Gantert, G. E.; Craig, W. E. *J. Am. Chem. Soc.* **1956**, *78*, 4965.

Diastereoselective Synthesis of (24*R*,25*S*)-5β-Cholestane-3α,24,26-triol[1]

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Sterols with hydroxylated side chains are important intermediates in the course of our studies directed toward the biochemical transformation of cholesterol to the bile acids. It is essential in these studies that the compounds be diastereomerically pure. Tedious separation of diastereomers from an epimeric mixture led us to explore more convenient methods.

This paper describes a synthetic approach to regio- and stereoselective access to chiral side-chain-hydroxylated sterols. Of particular interest is the appealing conversion of lithocholic acid (**1**) to (24*R*,25*S*)-5β-cholestane-3α,24,26-triol (**11**), a threo trihydroxylated steroid with chiral centers at C-24 and C-25.

The 3α-hydroxy group of lithocholic acid (**1**) was protected as the tetrahydropyranyl ether and the latter reduced with lithium aluminum hydride to the C-24 primary alcohol **2**, which was oxidized with pyridinium chlorochromate to yield 3α-[(tetrahydropyranyl)oxy]-5β-cholan-24-al (**3**), according to a previously published procedure.[3] Wittig condensation of the aldehyde **3** with methyl (triphenylphosphoranylidene)acetate under reflux in benzene gave the (24*E*)-conjugated ester **4**. A small amount (2%) of the (24*Z*)-conjugated ester **4z** was isolated by preparative TLC and characterized. Reduction of the (24*E*)-conjugated ester **4** with diisobutylaluminum hydride afforded the (24*E*)-allylic alcohol **5** in moderate yield.

The Sharpless procedure[4] for asymmetric epoxidation of allylic alcohols uniformly affords the respective enantiomer with high selectivity. Reaction of the (24*E*)-allylic alcohol **5** with anhydrous *tert*-butyl hydroperoxide in the presence of titanium tetraisopropoxide and D-(−)-diethyl tartarate gave the epoxide **6**. The configurarations at C-24

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