Synthesis of vicinal Iodothiocyanates, Iodoisothiocyanates, and Iodoazides using Phase-Transfer Reagents

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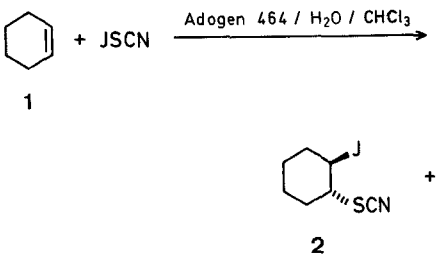
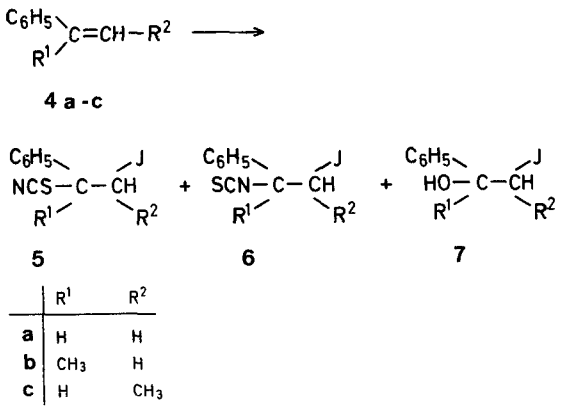
Recently we reported[1] methods for the electrophilic addition of iodine thiocyanate to alkenes which gave either a *vicinal* iodothiocyanate or *vicinal* iodoisothiocyanate as the major product. These reactions, which involved generation of the reagent from iodine(I) chloride/potassium thiocyanate, iodine/thallium(I) thiocyanate, or iodine/potassium thiocyanate, were effected in a solvent mixture of chloroform/sulpholane at 0°.

We have now found that if the reaction with iodine/potassium thiocyanate is carried out at ambient temperature, high yields are obtained using chloroform alone as solvent. Moreover, the rate of electrophilic addition of iodine thiocyanate is accelerated using water as a second phase and further increased by addition of the phase-transfer catalyst Adogen 464 [methyltrialkyl(C_8-C_{10}) ammonium chloride; supplier: Aldrich Chemical Company, Inc.]. Thus, after 2 h at 20° cyclohexene (1.25 mmol), iodine (3 mmol), and potassium thiocyanate (6.25 mmol) in chloroform (10 ml)/water (1 ml)/Adogen 464 (0.06 mmol) gave 43% of **2**+**3**, while reaction in chloroform/water or chloroform alone gave 24% and 11%, respectively.

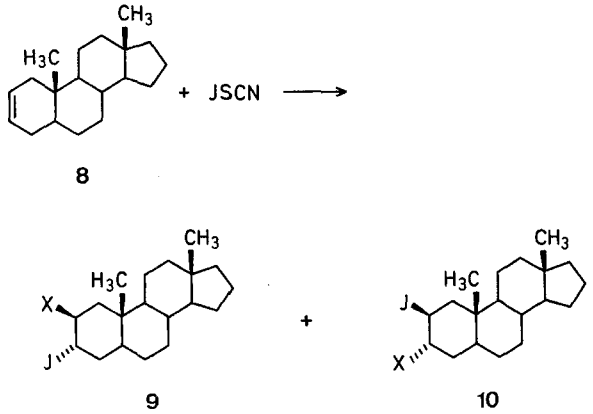


Other reactions with the biphasic solvent system and Adogen 464 are listed in the Table (see also Scheme A).

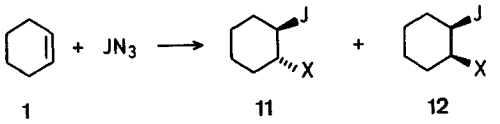


Scheme A

The rate acceleration was particularly evident with 5α-androst-2-ene (**8**) where the ratios of products to alkene after 94 h at 20° were 0.41:1 (chloroform), 1.7:1 (chloroform/water), and 15:1 (chloroform/water/Adogen 464). These reactions gave mixtures of regioisomers **9** (X=NCS) +**10** (X=NCS) (23%) and **9** (X=SCN) +**10** (X=SCN) (34%) from which pure samples of the major components **9** (X=NCS) and **9** (X=SCN) were obtained after purification. Compounds **9** (X=SCN) and **10** (X=SCN) reverted to the starting alkene both on standing and during separation by P.L.C. on silica gel.



The procedure has been extended to the synthesis of *vicinal* iodoazides without requiring the use of either iodine(I) chloride[2] or sulpholane[3]. Treatment of cyclohexene (**1**) with iodine and sodium azide in chloroform/water/Adogen 464 at 20° for 48 h resulted in 88% conversion to **11** (X=N_3) (50%), **12** (X=N_3) (4%), **11** (X=Cl) (4%), and **11** (X=OH) (10%). No iodoazide was formed in the absence of water and Adogen 464, and the formation of **11** (X=OH) was suppressed by doubling the amount of sodium azide.



The success of the above reactions stems from the high nucleophilicities of the anions used. In contrast, attempted iodoacetoxylation of cyclohexene (1.25 mmol) with iodine (3 mmol) and potassium acetate (12.5 mmol) in chloroform (10 ml)/water (1 ml)/Adogen 464 (0.06 mmol) gave only 9% of **11** (X=OAc) and 13% of **11** (X=OH) after refluxing for 45 h. In the absence of a second anion, however, use of chloroform/water (large excess) allowed high conversion (95%)[cf. 3] of cyclohexene into iodohydrin **11** (X=OH) after refluxing for 52 h irrespective of the presence of the phase-transfer catalyst.

18-Crown-6, which is frequently used as a solid-liquid phase transfer reagent[4] also increased the rate of electrophilic addition. Thus, stirring cyclohexene (1.25 mmol) iodine (3 mmol), potassium thiocyanate (6.25 mmol), and 18-crown-6 (20 mol-% of potassium thiocyanate)[4] in chloroform (10 ml) at 20° for 2 h gave 84% conversion (11% without 18-crown-6) to **2** (77%) and **3** (7%). 5α-Androst-2-ene (0.25 mmol) in chloroform (10 ml) gave 66% (33% without 18-crown-6) of **9** (X=SCN) and **10** (X=SCN) (2:1), with traces of **9** (X=NCS) and **10** (X=NCS) after 94 h at 20°.

The utility of the crown ether was particularly marked in the syntheses of iodoazides and iodoacetates, where there was no iodohydrin formation even although the reagents were not anhydrous. Cyclohexene (1.25 mmol), iodine (3 mmol), sodium azide (7.5 mmol), and 18-crown-6 (1.5 mmol) in chloroform gave only **11** (X=N_3) (100%) after 23 h at 20°, while 5α-androst-2-ene (94 h) gave a 3.4:1 mixture of **9** (X=N_3) and **10** (X=N_3) (68%) together with a 6:1 mixture of 3α-azido-2α-iodo-5α-androstane[5] and 2α-azido-3α-iodo-5α-androstane (10%). Under similar conditions but using potassium acetate, cyclohexene (47 h) gave 97% of **11** (X=OAc) whereas 5α-androst-2-ene afforded only 36% of **9** (X=OAc) after 100 h. With less potassium acetate or sodium azide much lower yields were obtained, and there was virtually no conversion to the respective adducts in the absence of 18-crown-6. A 57% yield of **11** (X=OAc) together with 5% of **11** (X=OH) was obtained without 18-crown-6 using acetonitrile as solvent with double the amount of iodine.

Addition of Iodine Thiocyanate to Cyclohexene; Typical Procedure: A solution of potassium thiocyanate (0.61 g, 6.25 mmol) in water (1 ml) is added to a mixture of iodine (0.76 g, 3.0 mmol) and Adogen 464 (0.03 g, 0.06 mmol) in ethanol-free chloroform. Cyclohexene (0.103 g, 1.25 mmol) is added dropwise to the biphasic system which is stirred at 20° in the dark for 2 h. Excess of iodine is then removed by shaking with an aqueous solution of sodium metabisulphite. Products are extracted with dichloromethane and the organic solution is passed through a short column of silica gel to remove Adogen 464. Solvent is removed in vacuo to give a mixture of **2** and **3** (0.145 g, 43%) as an oil which is separated by P.L.C. into *trans*-1-iodo-2-thiocyanatocyclohexane (**2**); yield: 30%:

$C_7H_{10}JNS$ calc. C 31.47 H 3.77 J 47.51 N 5.24
(267.1) found 31.50 3.59 48.32 5.26

I.R. (film): ν_{max}=2160 cm^{-1} (SCN).

^{1}H-N.M.R. (CCl_4): δ=3.52 (m, CHS), 4.34 ppm (m, CHJ).

^{13}C-N.M.R. ($CDCl_3$): δ=24.674, 26.232 (C-4 and C-5), 32.336, 32.726 (C-3 and C-6), 38.569 (C-1), 55.581 (C-2), 110.383 ppm (SCN).

and *trans*-1-iodo-2-isothiocyanatocyclohexane (**3**); yield: 13%;

$C_7H_{10}JNS$ (267.1) calc. C 31.47 H 3.77 J 47.51 N 5.24
found 31.60 3.59 48.20 5.41

I.R. (film): $\nu_{max} = 2060\,cm^{-1}$ (NCS).

^1H-N.M.R. (CCl_4): $\delta = 3.88$, 4.21 ppm (overlapping multiplets, CHN and CHJ, respectively).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 23.246$, 26.363 (C-4 and C-5), 31.817, 33.245 (C-3 and C-6), 37.271 (C-1), 62.984 (C-2), 133.109 ppm (NCS).

Addition of Iodine Thiocyanate to Cyclohexene using 18-Crown-6: 18-Crown-6 (0.33 g, 1.25 mmol) is added to anhydrous potassium thiocyanate (0.61 g, 6.25 mmol) in ethanol-free chloroform (10 ml) and the mixture is stirred for 10 min. Iodine (0.76 g, 3 mmol) and cyclohexene (0.103 g, 1.25 mmol) are then added and the mixture is stirred at 20° in the dark for 2 h in a moisture-free atmosphere. Work up as in the typical procedure above gives a pale yellow oil (0.282 g, 84%) containing *trans*-1-iodo-2-thiocyanatocyclohexane (**2**: 0.257 g, 77%), and *trans*-1-iodo-2-isothiocyanatocyclohexane (**3**: 0.025 g, 7%).

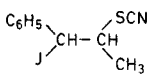
Addition of Iodine/Sodium Azide to Cyclohexene: A solution of sodium azide (0.41 g, 6.25 mmol) in water (1.5 ml) is added to a mixture of iodine (0.76 g, 3.0 mmol) and Adogen 464 (0.03 g, 0.06 mmol) in ethanol free chloroform (10 ml). Cyclohexene (0.103 g, 1.25 mmol) is added dropwise to the biphasic system which is stirred at 20° in the dark for 48 h. The resulting mixture is then worked up as in the typical procedure above to give an oil which is separated by P.L.C. into four fractions.

(a) *trans*-Azido-2-iodocyclohexane (**11**, X = N_3); yield: 50%; b.p. 75°/torr, (Lit.[6], 73–74°/0.90 torr).

I.R. (film): $\nu_{max} = 2100\,cm^{-1}$ (N_3).

^1H-N.M.R. (CCl_4): $\delta = 3.98$ (m, CHJ), 3.50 ppm (m, CHN_3).

Table. Iodothiocyanate and Iodoisothiocyanate Derivatives

Substrate	Products	Molecular formula	Yield [%][a]	Reaction Time
1	**2**	$C_7H_{10}JNS$[b] (267.1)	61	22 h
	3		17	
4a	**5a**	C_9H_8JNS (289.0)	55	24 h
	6a	C_9H_8JNS (289.0)	14	
	7a	C_9H_6JO (247.9)	1	
4b	**5b**	$C_{10}H_{10}JNS$ (303.0)	71	49 h
	7b	$C_{10}H_{11}JO$ (261.9)	4	
	elimination and substitution products		6	
4c	**5c**	$C_{10}H_{10}JNS$ (303.0)	31	46 h
	7b	$C_{10}H_{11}JO$ (261.9)	2	
		unstable	18	

[a] Yield of product isolated by preparative layer chromatography (P.L.C.). All other yields in this paper are calculated from ^1H-N.M.R. analysis of the crude product.

[b] All products gave satisfactory microanalyses (C ±0.3%, H ±0.35%, N ±0.25%, J ±0.8%). Analyses were carried out by Prof. A. D. Campbell and Associates, University of Otago, New Zealand.

(b) *cis*-1-Azido-2-iodocyclohexane (**12**, X = N_3); yield: 4%;

I.R. (film): $\nu_{max} = 2100\,cm^{-1}$ (N_3).

^1H-N.M.R. (CCl_4): $\delta = 3.19$ (m, CHN_3), 4.46 ppm (m, CHI).

M.S.: $m/e = 251$ ($M^{+\bullet}$).

The product was identical with a hitherto unidentified product from the action of sodium azide/iodine on cyclohexene[5].

(c) *trans*-1-Chloro-2-iodocyclohexane[5] (**11**, X = Cl) (4%).

^1H-N.M.R. (CCl_4): $\delta = 4.24$–4.77 ppm (overlapping multiplets, CHCl and CHJ).

M.S.: $m/e = 246$, 244 (ca. 1:3) ($M^{+\bullet}$).

(d) *trans*-2-Iodocyclohexan-1-ol (**11**, X = OH) (10%).

$C_6H_{11}JO$ (226.1) calc. C 31.86 H 4.91 J 56.15
found 31.83 4.78 55.91

I.R. (film): $\nu_{max} = 3400$–$3600\,cm^{-1}$ (OH).

^1H-N.M.R. (CCl_4): $\delta = 3.32$–4.34 ppm (overlapping multiplets, CHOH and CHI).

M.S.: $m/e = 226$ ($M^{+\bullet}$).

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