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Simple Stereospecific Synthesis of *endo*-Norbornyl Chloride

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Received December 12, 1978

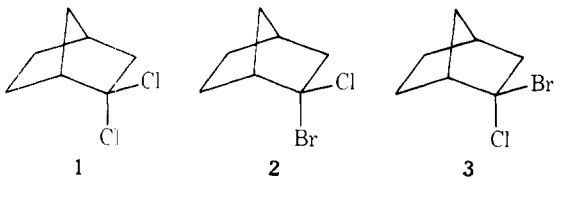
exo-Norbornyl chloride can be prepared easily in very high isomeric purity by the addition of hydrogen chloride to norbornene.[2] However, difficulties have been encountered in preparing *endo*-norbornyl chloride free of the epimeric exo compound.

Roberts and his co-workers[3] synthesized *endo*-norbornyl chloride by the hydrogenation over PtO_2 of 5-chloro-2-norbornene prepared by the Diels–Alder condensation of cyclopentadiene with vinyl chloride. However, solvolytic studies revealed that it was contaminated with the more reactive *exo*-chloride. Indeed, the product proved to be a mixture of 87% *endo*- and 13% *exo*-chloride. Repeated solvolysis of the above mixture ultimately yielded *endo*-chloride of 95% purity.[4]

In the literature several other procedures for preparing *endo*-norbornyl chloride have been reported. However, none of these procedures yields the isomerically pure compound. Free-radical chlorination of norbornane gives predominantly the 2-chlorides, with exo/endo product ratios depending upon the precise nature of the chlorine donor.[5] Thus, molecular chlorine gives about 70% exo and 20–25% endo. The more selective chlorinating agents, SO_2Cl_2, CCl_4, and PCl_5, give approximately 95% exo.

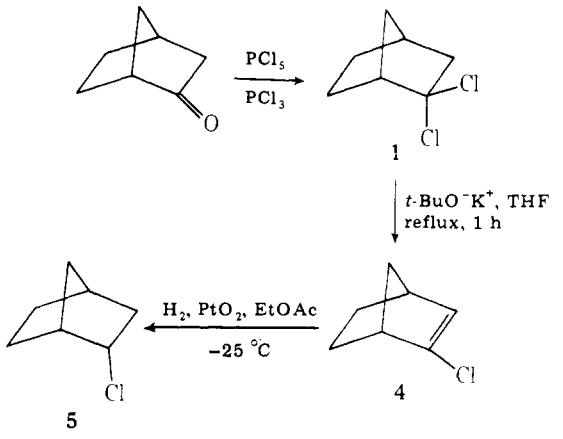
The reaction of *exo*-norbornanol with triphenylphosphine and carbon tetrachloride gives the 2-norbornyl chlorides in a molar ratio of 3.8–3.5:1.0 exo/endo.[6]

The controlled potential electrochemical reduction[7] at a mercury cathode of 2,2-dichloronorbornane (**1**), *exo*-chloro-*endo*-bromonorbornane (**2**), or *exo*-bromo-*endo*-chloronorbornane (**3**) gave similar mixtures of *endo*-norbornyl chloride (36–80%) and nortricyclane (64–20%).



1 2 3

Scheme I



Cristol and his co-workers[8] established that the photosensitized irradiation of purified *endo*-chloronorbornene with a variety of sensitizers and solvents led to the saturation of the double bond to form *endo*-norbornyl chloride in yields of approximately 10%.

Brown and De Lue[9] observed that the reaction of nitrogen trichloride with tri-*exo*-norbornylborane gave a mixture of the two epimeric chlorides, 77% *exo*- and 23% *endo*-chloride.

For our solvolytic studies we desired to utilize isomerically pure *endo*-norbornyl chloride. Since none of the published procedures would give us the pure endo compound, we undertook to prepare *endo*-norbornyl chloride (**5**) by a stereospecific route, as illustrated in Scheme I. 2,2-Dichloronorbornane (**1**) was prepared following the literature procedure[10] and converted into 2-chloronorbornene (**4**) by a modified procedure which reduced the reaction time from 40 to 1 h.[11] Next, 2-chloronorbornene was hydrogenated in ethyl acetate using PtO_2 as catalyst in a Brown hydrogenator.[12] When the hydrogenation was carried out at 25 °C, considerable reductive dehalogenation was observed. In order to minimize reductive dehalogenation, the low-temperature procedure developed by C. A. Brown[13] was utilized. He had observed that the rates of hydrogenation of olefins were remarkably insensitive to decreases in the temperature of hydrogenation. Even more important, such hydrogenations at lower temperatures show considerable improvements in the selectivity of the reaction. Indeed, as the temperature of hydrogenation of 2-chloronorbornene was lowered, less and less reductive dehalogenation was observed. GC analysis of the product hydrogenated at −25 °C revealed a yield of *endo*-norbornyl chloride of 90%. There was readily isolated an 82% yield of the pure product, mp 44–45 °C. These results are summarized in Table I.

The product, *endo*-norbornyl chloride, was examined carefully, both by ^{13}C and ^{1}H NMR spectroscopy, and was evidently free of the epimer.

Table I. Hydrogenation of 2-Chloronorbornene. Effect of Temperature on the Selectivity of Hydrogenation

		% product[c]	
temp,[a] °C	$T_{100\%}$, min[b]	*endo*-norbornyl chloride[e]	norbornane[f]
25	60	62	38
0	100	70	30
−10	135	75	25
−25	200	90 (82)[d]	10

[a] Temperatures were held to ±1 °C. [b] Time for complete reduction. [c] GC yield. [d] Isolated yield. [e] Registry no., 2999-06-6. [f] Registry no., 279-23-2.

0022-3263/79/1944-1348$01.00/0

This is the first stereospecific synthesis of pure *endo*-norbornyl chloride. It appears to provide the basis for a general procedure for the synthesis of such *endo*-bicyclic chlorides.

Experimental Section

The melting and boiling points are uncorrected. The ^1H NMR and ^{13}C NMR spectra were recorded on Varian T-60 and Varian FT-80A spectrometers, respectively.

Preparation of 2,2-Dichloronorbornane (1). 2,2-Dichloronorbornane was made, following the reported procedure,[10] in 60% yield, bp 70–72 °C (14 mm) [lit.[10] bp 65–68 °C (12–12.4 mm)].

Preparation of 2-Chloronorbornene (4). This was made by a modification of the reported procedure.[11] In an oven-dried, nitrogen-flushed, 250-mL round-bottom flask fitted with a septum inlet, a magnetic stirring bar, and a reflux condenser topped with a connecting tube leading to a mercury bubbler was placed potassium *tert*-butoxide (16.8 g, 150 mmol). Dry THF (100 mL) was added. To this well-stirred solution was added 2,2-dichloronorbornane (16.6 g, 100 mmol). This mixture was heated under reflux for 1 h (the reaction was complete as indicated by the absence of the peak due to 2,2-dichloronorbornane in the GC analysis of an aliquot). The reaction mixture was cooled, poured into water (200 mL), and extracted with pentane (3 × 100 mL). The combined organic layers were washed with water (5 × 100 mL) and dried over anhydrous sodium sulfate. Solvent was removed, and the residue was distilled to provide pure 2-chloronorbornene in a yield of 90% (11.6 g), bp 62–63 °C (57 mm) [lit.[11] bp 72–73 °C (69 mm)].

***endo*-Norbornyl Chloride (5).** The hydrogenation of 2-chloronorbornene was carried out using the Ace Brown hydrogenator.[12] In the reactor flask was placed 2-chloronorbornene (1.29 g, 10 mmol), ethyl acetate (20 mL), and platinum oxide[14] (100 mg). Hydrogen was generated using a solution of sodium borohydride in Me_2SO (~1 M) added to aqueous acetic acid. After the absorption of hydrogen ceased, the catalyst was removed by filtration through a sintered glass funnel. The solvent was then removed, and the residue was distilled to provide the pure *endo*-norbornyl chloride: bp 88–90 °C (110 mm); mp 44–45 °C [lit.[3] bp 51–53 °C (17 mm), mp 34–36 °C].

Anal. Calcd for $C_7H_{11}Cl$: C, 64.12; H, 8.4; Cl, 27.48. Found: C, 64.40; H, 8.63; Cl, 27.46.

The hydrogenation was carried out at 25, 0, −10, and −25 °C. The results are summarized in Table I.

Registry No.—1, 19916-65-5; 4, 694-93-9.

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New Synthetic Approaches to 4(1*H*)-Pyridinone Derivatives. 3.[1] 2-Bromoacetylated Enamines as Pyridine Ring Synthons

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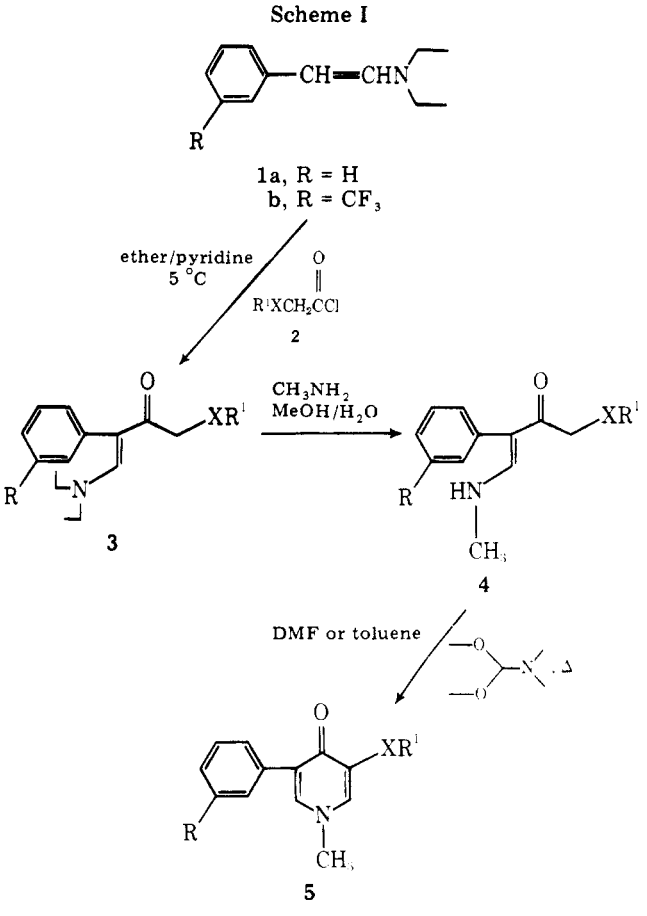
Received September 6, 1978

The synthesis of highly functionalized pyridines by conceptually differing routes continues to draw the attention of numerous research groups.[2-10] We[1] and others[11] have recently described methods for synthesizing 3,5-disubstituted-4(1*H*)-pyridinone compounds. This paper describes the synthesis of pyridinone rings bearing heteroatoms (O, S, N, Cl, and Br) in the 3 position.

Scheme I



	R	R^1	X	mp, °C	yield, %[12]
5a	H	C_6H_5	S	164–165	18
5b	CF_3	C_6H_5	S	151–152	16
5c	H	C_6H_5	O	176–177	19
5d	CF_3	C_6H_5	O	144–145	17
5e	H	CH_3	O	153–155	23
5f	CF_3	CH_3	O	173–175	18

Acylation of a dialkylstyrylamine (1) with an acid chloride (2) R^1XCH_2COCl in anhydrous ether (Linde 4Å sieves) in the presence of pyridine, at 5 °C over a 4-h period, gave enaminone **3**. Enamine exchange with aqueous methanolic methylamine in 40 min to 2 h gave the *N*-methylenaminones **4**, which were cyclized by refluxing with *N,N*-dimethylformamide dimethyl acetal, neat or in DMF or toluene, to the pyridinones **5** (Scheme I).

We next turned our attention toward preparing 3-substituted pyridinones starting with phenylacetone derivatives.

The process of Scheme II was applied to the synthesis of 3-bromo- and 3-chloro-4(1*H*)-pyridinones. Pyridinones **5g** and **5h** were obtained in 26 and 16% overall yields based on the corresponding phenylacetones **6**. Though **5g** and **5h** could be readily halogenated with aqueous halogen at 30 °C to give the pyridinones **5i–5k** in moderate to good yields, the halogen atoms in the 3 position were quite recalcitrant to nucleophilic displacement.[13] However, bromoacylation of diethylstyrylamines readily afforded the bromoacetylated enamines **8** in excellent yields (85–90% in 2 h at 5–10 °C, ether solvent, without special precautions). The bromine atom in **8** was readily displaced by a variety of alkylthio anions and by secondary amines to give the enaminones **9**, which were readily

0022-3263/79/1944-1349$01.00/0