Synthesis of Certain Cyclopropylpyridines

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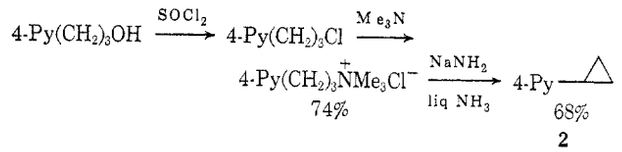
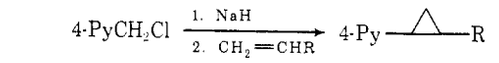
A series of cyclopropylpyridines has been prepared by a new route and their possible participation in nucleophilic ring-opening reactions has been investigated.

Prior to our work the synthesis of 2- and 4-cyclopropylpyridine as well as certain of their ring-substituted derivatives had been reported.[2,3] Mariella, *et al.*,[2] prepared 2-cyclopropylpyridine (1) *via* a six-step process in a 3% overall yield starting with methyl cyclopropyl ketone. Since doubt was expressed[3] as to whether **1** had actually been obtained, an unequivocal synthesis of crude **1** (54%) from 2-(2-pyridyl)-1,3-propanediol was subsequently reported.[4] 4-Cyclopropylpyridine (2) has been prepared[3] by the following route.



4-Py = 4-pyridyl group

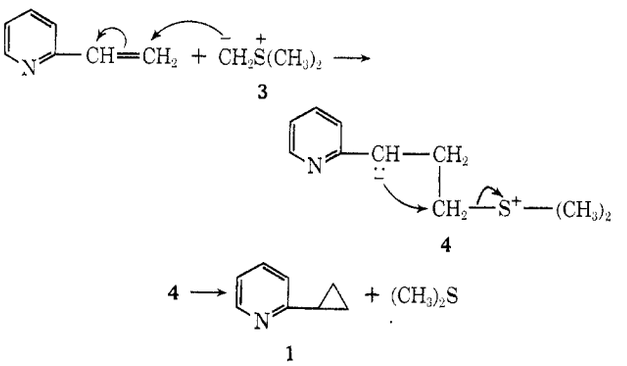
Several 2- and 4-cyclopropylpyridine derivatives have also been reported. Burger, *et al.*,[5] obtained 2-(2-carbethoxycyclopropyl)pyridine (63%) from 2-vinylpyridine and ethyl diazoacetate. More recently[3] a series of 4-cyclopyridine derivatives has been prepared.



R = CO_2CH_3 (54%), $CO_2C_2H_5$ (60%), CN (18%)

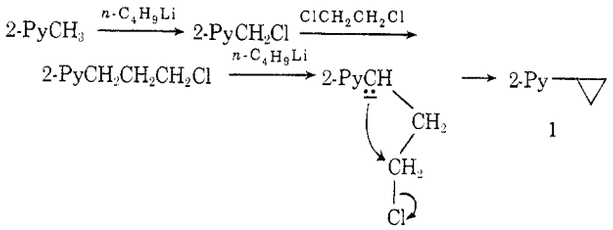
We now report a different route to **1** and **2**, the previously reported 2- and 4-cyclopropylpyridines, and other related systems which are apparently not reported in the literature. Previously, Corey and Chaykovsky[6] observed that dimethylsulfonium methylide (**3**) reacts with activated olefins to give cyclopropanes. Thus, **3** reacts with 1,1-diphenylethylene to give 1,1-diphenylcyclopropane (60%).[6] We have found that **3** reacts with a variety of 2- and 4-vinylpyridines to give the corresponding cyclopropanes (40–91%). Of all the vinylpyridines studied apparently the olefinic bond of only 3-methyl-5-vinylpyridine is too inactive to react with **3**. The cyclopropanes which were prepared appear in Table I.

The reaction of **3** with the 2- and 4-vinylpyridine systems can be envisioned as a Michael-type condensation[7] to give an intermediate carbanion **4**, which



undergoes an intramolecular displacement on carbon with the loss of dimethyl sulfide and the formation of the cyclopropane ring.

Two other methods were attempted as possible routes to cyclopropylpyridines. The Simmons–Smith[8,9] type reaction involving 2-vinylpyridine, methylene bromide, and a zinc–copper couple failed to give any 2-cyclopropylpyridine. The reaction of 1 equiv of 2-picoline and 1,2-dichloroethane with 2 equiv of *n*-butyllithium in THF gave a very low yield (5.3%) of 2-cyclopropylpyridine (**1**), apparently as shown.



2-Py = 2-pyridyl group

Certain activated cyclopropanes, *e.g.*, 1,1-dicarbethoxy-[10] and 1-cyano-1-carbethoxycyclopropane,[11] are susceptible to nucleophilic ring opening. Therefore, it was of interest to determine whether a pyridyl substituent could sufficiently activate cyclopropane so that it would undergo nucleophilic ring opening.

When 4-cyclopropylpyridine was treated with sodiomalonic ester and *n*-butyllithium, ring opening did not occur. The former reaction gave only recovered starting materials, while the latter reaction gave 2-*n*-butyl-4-cyclopropylpyridine (65%), which apparently arises from the addition of *n*-butyllithium to the azomethine linkage of the pyridine ring followed by the loss of lithium hydride. The fact that azomethine addition rather than ring opening occurred may have some interesting synthetic overtones.

(1) Based on the thesis submitted by G. R. P. to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(2) R. P. Mariella, L. F. A. Petersen, and R. C. Ferris, *J. Amer. Chem. Soc.*, **70**, 1494 (1948).

(3) A. P. Gray and H. Kraus, *J. Org. Chem.*, **31**, 399 (1966).

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(5) A. Burger, D. G. Markees, W. R. Nes, and W. L. Yost, *J. Amer. Chem. Soc.*, **71**, 3307 (1949).

(6) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

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(8) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(9) E. LeGoff, *J. Org. Chem.*, **29**, 2048 (1964).

(10) R. W. Kierstad, R. P. Linsted, and B. C. L. Weedon, *J. Chem. Soc.*, 3616 (1952).

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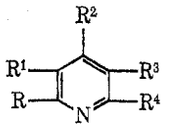
TABLE I

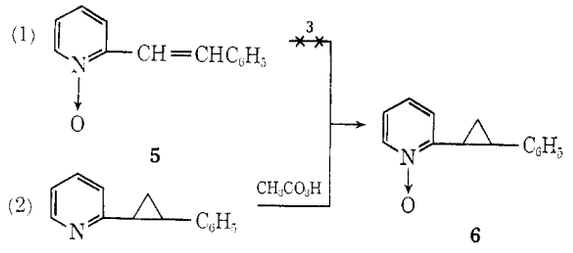
CYCLOPROPYLPYRIDINES AND THEIR *N*-OXIDES



Registry no.	Compd[a]	R	R¹	R²	R³	R⁴	Bp, °C (mm)	Yield, %	Picrate[a] mp, °C	Picrate registry no.
20797-87-9	1	H	H	H	H	c-C_3H_5	67–70 (20)[b]	40.0	129.4–130.7	41764-98-1
4904-21-6	2	H	H	c-C_3H_5	H	H	74–76 (6)	65.4	170.8–171.8[c]	
41765-00-8	3	CH_3	H	H	H	c-C_3H_5	82–83 (20)[d]	78.0	154.8–156.2	41765-01-9
41765-02-0	4	H	C_2H_5	H	H	c-C_3H_5	107 (19)[e]	65.0	135.1–135.6	41864-64-6
41765-03-1	5	H	H	c-C_3H_4Ph	H	H	200–202 (20)	81.0	173.6–175.2	41765-04-2
41764-76-5	6	H	H	H	H	c-C_3H_4Ph	175–177 (14)[f]	70.0	201–202.4	41764-77-6
41764-78-7	7	H	H	c-C_3H_4Ph	CH_3	H	139.5–141 (0.5)	91.0	146.6–148.4	41764-79-8
41764-80-1	8	H	H	H	CH_3	c-C_3H_4Ph	133.5–135 (0.7)[g]	58.0	202–203	41764-81-2
41764-82-3	9[h]						163.4–164.6[k]	65.8		
41764-83-4	10[i]						75–77[k]	38.4		
41764-84-5	11[j]						112–8–113.8[k]	52.2		

[a] Satisfactory analytical data (±0.4% for C and H for the compounds and N for the picrates) were obtained for all the compounds listed in the table. [b] The product was shown to be a mixture of vinylpyridine and 1. The yields were determined by glc, which showed that the product was either a pure cyclopropylpyridine or a mixture of cyclopropylpyridine and recovered pyridylalkene. [c] This is a hydrochloride, lit.[3] mp 170.0–171.0°. [d] Glc showed the product to be a mixture of 2-methyl-6-vinylpyridine and 3. [e] Glc showed the product to be a mixture of 2-vinyl-5-ethylpyridine and 4. [f] Glc showed the product to be a mixture of 2-styrylpyridine and 6. [g] Glc showed the product to be a mixture of 3-methyl-2-styrylpyridine and 8. [h] This is the *N*-oxide of compound 2. [i] This is the monohydrate of the *N*-oxide of compound 5. [j] This is the *N*-oxide of compound 6. [k] Melting point.

The failure of 4-cyclopropylpyridine to undergo nucleophilic ring opening prompted the investigation of an *N*-oxide in such a reaction, since the NO group can act as an electron acceptor.[12] Two possible routes to cyclopropylpyridine *N*-oxides were examined.



It was found that when 2-styrylpyridine *N*-oxide (**5**) was treated with **3** (route 1) none of the desired 1-phenyl-2-(2-pyridyl)-cyclopropane *N*-oxide (**6**) was obtained using THF as a reaction medium and only a 3.5% yield was obtained in DMSO. By contrast, route 2 (the peracetic acid oxidation of preformed pyridylcyclopropanes) gave fair to good yields of **6** (52.2%) and two other derivatives (Table I, compounds 9–11).

However, refluxing an ethanolic mixture of **6** and sodiomalonic ester for 29 hr gave a quantitative recovery of starting materials. Apparently the *N*-oxide function is not a powerful enough activator to assist in the cyclopropane ring opening, at least with this nucleophile.

Experimental Section

Starting Materials.—The 2-methyl-5-vinylpyridine was supplied through the courtesy of Phillips Petroleum Co., Bartlesville, Okla., while the 2- and 4-picoline, 2,3- and 2,4-lutidine, 2- and 4-vinylpyridine, 2-methyl-6-vinylpyridine, and 2-vinyl-5-ethylpyridine were generously supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Corp., Indianapolis, Ind. The *n*-butyllithium was kindly supplied by Dr. W. T. Barrett, Foote Mineral Co., Exton, Pa. The various styrylpyridines were prepared by the method of Williams, *et al.*[13] Pentimalli's[14] route to 2-styrylpyridine *N*-oxide was used.

Characterization of Reaction Products.—Glc analysis of the various product mixtures was carried out on either a 12-ft copper column consisting of 12% Carbowax 20M and 8% Carbowax 1500 on an 80–100 mesh Chromosorb P solid support or a 20 ft × 0.375 in. 30% SE-30 preparative column. Temperatures for the column, injection port, and block were adjusted to give good analyses for the components which were being analyzed.

General Procedure for the Synthesis of Cyclopropylpyridine Derivatives Using 4-Cyclopropylpyridine (2) as an Example.—Trimethylsulfonium iodide[15] (0.06 mol, 12.24 g) was added to 100 ml of dry THF in a three-neck, round-bottom flask fitted with a water-cooled condenser (Drierite tube) and a magnetic stirrer. The flask was cooled in an ice–salt bath to 0° or lower and *n*-butyllithium in hexane (0.04 mol, 24.8 ml) was added, under nitrogen, *via* a syringe, to the rapidly stirred suspension of the trimethylsulfonium iodide, maintaining the temperature around 0°. The mixture was stirred for 10 min after the addition of the *n*-butyllithium was completed and then 4-vinylpyridine (0.04 mol, 4.20 g) in 50 ml of THF was added over a 10-min period. The reaction mixture was stirred for 1 hr at 0°, the ice–salt bath was removed, and stirring was continued for 3 hr at ambient temperature. The THF was removed by a rotoevaporator, and the residue was poured into water (tested basic to litmus) and extracted with several portions of $CHCl_3$. The water treatment caused the precipitation of polymerized material, which was filtered. The combined $CHCl_3$ extracts were dried (Na_2SO_4), the solvent was removed at atmospheric pressure, and the residue was distilled under vacuum to give 3.08 g of material, bp 74–76° (6 mm). Glc analysis of this material gave one peak with a longer retention time than that of an authentic sample of 4-vinylpyridine. This 3.08 g of material was collected preparatively using glc for characterization and when treated with ethereal hydrogen chloride it gave a hydrochloride, mp 170.8–171.8° (from isopropyl alcohol–ether) (lit.[3] mp 170–171°). A 65.4% yield of 4-cyclopropylpyridine (**2**) was obtained.

General Procedure for the Synthesis of Cyclopropylpyridine *N*-Oxides Using 4-Cyclopropylpyridine *N*-Oxide as an Example.—4-Cyclopropylpyridine (0.02 mol, 2.38 g) was added to glacial acetic acid (25 ml) and 30% hydrogen peroxide (3 ml) and the mixture was stirred for 6 hr at 70–80° followed by the removal of the acid at reduced pressure (rotoevaporator). The mixture was poured into water, and the aqueous phase was made basic

(12) A. R. Katritzky, *Quart. Rev., Chem. Soc.*, **10**, 395 (1956).

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(14) L. Pentimalli, *Tetrahedron Lett.*, **No. 14**, 151 (1961).

(15) H. J. Emeleus and H. G. Heal, *J. Chem. Soc.*, 1126 (1946).

(aqueous Na_2CO_3) and extracted with several portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and, after the $CHCl_3$ was removed at atmospheric pressure, the residue contained recovered 4-cyclopropylpyridine (0.65 g, 27.4% by comparison of its ir spectrum with that of an authentic sample) and 4-cyclopropylpyridine *N*-oxide (1.75 g, 65.8%, mp 163.4–164.6° from benzene). The structure of the product was confirmed by its elemental analysis, ir spectrum, and nmr spectrum.

Reaction of 4-Cyclopropylpyridine with *n*-Butyllithium.—4-Cyclopropylpyridine (0.02 mol, 2.38 g) was added to *n*-butyllithium (0.02 mol, 12.4 ml) and 100 ml of THF. The mixture was refluxed for 6 hr and cooled to room temperature and the THF was removed under reduced pressure (rotoevaporator). The residue was poured into water and extracted with several portions of $CHCl_3$ and the combined extracts were dried ($NaSO_4$). The solvent was removed at atmospheric pressure and the residue was vacuum distilled to give (1) recovered 4-cyclopropylpyridine, bp 74–76° (6.0 mm), 0.19 g, 8%, and (2) 2.06 g of material, bp 119–130° (5.6 mm). Glc analysis of fraction 2 showed three peaks. The peak with the shortest retention time corresponds to the retention time of an authentic sample of 4-cyclopropylpyridine. The smallest peak with an intermediate retention time was not identified. The largest peak with the longest retention time is 2-*n*-butyl-4-cyclopropylpyridine (65% based on glc analysis).

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 81.83; H, 9.65.

The picrate had mp 92.4–94.0° (from absolute ethanol). *Anal.* Calcd for $C_{18}H_{20}N_4O_7$: N, 13.86. Found: 13.86.

Registry No.—**3**, 6814-64-8; 2-vinylpyridine, 100-69-6; 4-vinylpyridine, 100-43-6; 2-methyl-6-vinylpyridine, 1122-70-9; 2-vinyl-5-ethylpyridine, 5408-74-2; 4-styrylpyridine, 103-31-1; 2-styrylpyridine, 714-08-9; 3-methyl-4-styrylpyridine, 13673-34-2; 3-methyl-2-styrylpyridine, 7433-87-6; 2-*n*-butyl-4-cyclopropylpyridine, 41764-88-9; 2-*n*-butyl-4-cyclopropylpyridine picrate, 41764-89-0.

Strained Ring Systems. XIV.[1a] Solvolysis of Arenesulfonate Derivatives of Benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol

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The buffered acetolysis and formolysis of benzobicyclo[2.2.0]hex-5-en-*exo*-2-yl tosylate (1-OTs) and nosylate (1-ONs) were investigated. Buffered acetolysis of 1-OTs produced only naphthalene while 1-ONs yielded naphthalene (58%) and benzobicyclo[2.1.1]hex-2-en-*exo*-5-yl acetate (2-OAc, 37%). Buffered formolysis of 1-ONs gave exclusively 2-O_2CH in 97% yield. The effects of the benzo group in 1 are discussed.

We recently published the synthesis of benzobicyclo[2.2.0]hex-5-en-*exo*-2-ol (1-OH) by hydroboration–oxidation of benzobicyclo[2.2.0]hexa-2,5-diene.[2] We now wish to report the preparation and results of solvolytic studies of the tosylate (1-OTs) and nosylate (1-ONs) esters.

Alcohol 1-OH was converted into arenesulfonates 1-OTs and 1-ONs by standard methods. As is our practice with new substrates such as these, approximate rates of buffered acetolysis were determined at two temperatures with two weighed samples (0.005 *M* ROX, 0.006 *M* KOAc) each of 1-OTs and 1-ONs in separate ampoules using the sealed ampoule technique. These approximate rate constants are generally within ±10% of values determined for first-order rate constants from a full kinetic run.[3] These rate constants are listed in Table I.

Table I

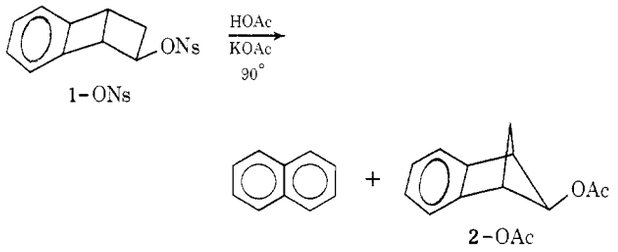
Approximate Buffered Acetolysis Rate Constants for 1-OTs and 1-ONs[a]

Compd	Temp, °C	k,[a] sec^{-1}
1-OTs	90.0	1.8×10^{-5}
	120.0	4.2×10^{-4}
1-ONs	70.0	4.6×10^{-6}
	90.0	4.7×10^{-5}

[a] Determined from only two kinetic points. The instantaneous rate constants from each point based on the initial concentration of substrate agreed within ±3% of these figures.

It was immediately obvious that more than a simple solvolysis reaction was occurring in either 1-OTs or 1-ONs or both from the ratio $k_{1\text{-ONs}}/k_{1\text{-OTs}} = 2.6$. We had previously found the nosylate–tosylate rate ratio to be about 10 for "normal" solvolyses for several primary derivatives,[4] and the same rate ratio was expected for these secondary derivatives.

Isolation of the materials from an interrupted buffered acetolysis of 1-OTs showed the presence of 1-OTs, naphthalene, and decomposition material. A preparative buffered acetolysis of 1-ONs at 90° for approximately 10 solvolytic half-lives (based on approximate k, Table I) yielded naphthalene (58%) and benzobicyclo[2.1.1]hex-2-en-*exo*-5-yl acetate (2-OAc, 37%).[5]



The thermal stabilities of 1-OTs and 1-ONs were determined by heating them in hydrocarbon solvents for the time required for approximately 10 buffered acetolysis half-lives of that arenesulfonate. Heating 1-OTs in xylene at 120° and 1-ONs in toluene at 90° produced naphthalene and the corresponding arenesulfonic acid in excellent yields with no recovery of the starting arenesulfonate. From these results it was

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(2) R. N. McDonald, D. G. Frickey, and G. M. Muschik, *J. Org. Chem.*, **37**, 1304 (1972).

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