

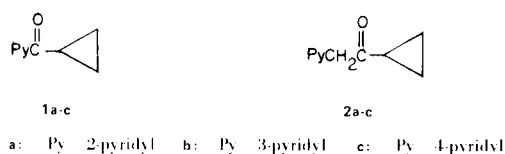
## The Synthesis of Pyridyl and Picolyl Cyclopropyl Ketones

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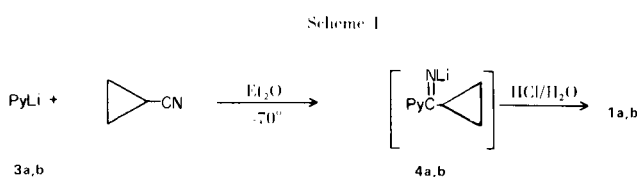
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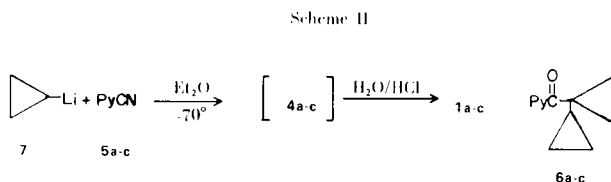
During the course of our work on the synthesis of alkaloids of *Nicotiana Tabacum*, we found it necessary to prepare the cyclopropyl pyridyl ketones (**1a-c**) and the cyclopropyl picolyl ketones (**2a-c**).



Since McCarty (1) had previously prepared **1a** in 32% yield by reaction of 2-pyridyllithium (**3a**) with cyclopropyl cyanide followed by hydrolysis of the intermediate ketimine (**4a**), we examined this method (Scheme I) as a route to **1b** (2).



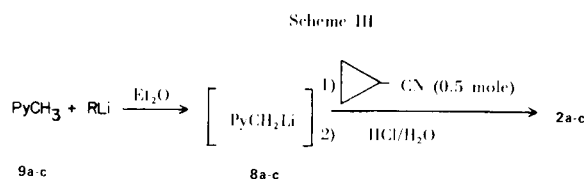
Reaction of 3-pyridyllithium (**3b**) with cyclopropyl cyanide gave cyclopropyl 3-pyridyl ketimine (**4b**) (4) which was hydrolyzed *in situ* to give **1b** in 25% yield. Since the instability of the pyridyllithiums (**3a,b**) was felt to be a major reason for the low yields of **1a** and **1b** (5), we explored the alternate synthesis illustrated in Scheme II (6).



Since its initial synthesis by Hart (7), cyclopropyl-lithium (**7**) has received scant attention as an organometallic reactant (8). Using the method of Seyferth (9) with minor modification, it was found that **7** could be prepared readily in large quantity. Reaction of **7** with the cyanopyridines (**5a-c**) proceeded smoothly at  $-70^\circ$  to give **4a-c** which were hydrolyzed *in situ* to **1a-c** in 65-85%

yield. A second product was isolated in low yield in each case. Based on spectral evidence, these products have been tentatively identified as 1-bicyclopropyl pyridyl ketones, **6a-c**. The mode of formation of **6a-c** is under investigation and will be reported subsequently.

Cyclopropyl 4-picolyl ketone (**2c**), prepared by Brust (10) *via* reaction of cyclopropanecarbonyl chloride with 4-picolyllithium (**8c**), was the only member of the series **2a-c** previously synthesized. In order to avoid possible problems with secondary reaction leading to carbinol formation (11) which might arise using cyclopropanecarbonyl chloride, we chose to explore the synthesis as outlined in Scheme III.



Although 2-picolyllithium (**8a**), readily formed from 2-picoline (**9a**), reacted smoothly with cyclopropyl cyanide to give **2a** (12), initial difficulties were encountered in the preparation of **8c**. It has been reported that **8c** can be formed in good yield by reaction of 4-picoline (**9c**) with methyllithium (13) or phenyllithium (14), but in our hands both lithium reagents gave large amounts of pyridine substitution products (13, 14) as well as the desired **8c**. Recent work by Serettas (15) has shown that if 2-thienyllithium (**10**) was used to form **8a-c** from **9a-c** in a tetrahydrofuran-benzene solvent mixture, subsequent reaction *in situ* with ketones gave essentially quantitative yields (based on **10**) of picolyl tertiary alcohols. Using this method to generate **8c**, a 20% yield of **2c** was obtained (16). Since it appeared that the complexation of **8c** with tetrahydrofuran (15) might be inhibiting its ability to react with cyclopropyl cyanide, the reaction was carried out in diethyl ether. Under these conditions **2c** was obtained in 40-50% yield. When 3-picoline (**9b**) was allowed to react with **10** (15) and the resultant reaction mixture treated with cyclopropyl cyanide, only a mixture of cyclopropyl 2-thienyl ketone (17) and its ketimine (18) (**11**) were obtained (19). Since 2-thienyllithium did not react in diethyl ether with **9b** to give **8b**,

Table I

## Physical Data

Compound Number	Yield %	M.p., °C or b.p., °C (mm.)	Ir in cm <sup>-1</sup> (a)	Pmr in δ (b)	Formula	Analyses		
						Calcd./Found C	H	N
<b>1a</b>	73	33-34.5 (c,d)	1688	1.11 (m, 4), 3.58 (m, 1),	C <sub>9</sub> H <sub>9</sub> NO	73.5	6.2	9.5
				7.69 (m, 3), 8.65 (m, 1) (e)		73.4	6.1	9.6
<b>1b</b>	63	80-1 (0.79)	1690	1.16 (m, 4), 2.63 (m, 1),	C <sub>9</sub> H <sub>9</sub> NO	73.5	6.2	9.5
				7.33 (m, 1), 8.16 (m, 1), 8.59 (m, 1), 9.19 (m, 1)		73.5	6.3	9.6
<b>1c</b>	86	65 (0.03)	1690	1.10 (m, 4), 2.60 (m, 1),	C <sub>9</sub> H <sub>9</sub> NO	73.5	6.2	9.5
				7.68 (m, 2), 8.68 (m, 2)		73.3	6.2	9.3
<b>2a</b>	86	67-8 (0.15)	1705	0.97 (m, 4), 2.06 (m, 1),	C <sub>10</sub> H <sub>11</sub> NO	74.5	6.9	8.7
				3.97 (s, 2), 7.32 (m, 3), 8.42 (m, 1)		74.3	7.0	8.5
<b>2b</b>	23	74-5 (0.06)	1710	0.90 (m, 4), 2.00 (m, 1),	C <sub>10</sub> H <sub>11</sub> NO	74.5	6.9	8.7
				3.84 (s, 2), 7.20 (m, 1), 7.55 (m, 1), 8.47 (m, 2)		74.7	6.9	8.8
<b>2c</b>	38	62-4 (f,g)	1710	0.90 (m, 4), 1.88 (m, 1),	C <sub>10</sub> H <sub>11</sub> NO	74.5	6.9	8.7
				3.71 (s, 2), 6.99 (m, 2), 8.44 (m, 2) (e)		74.5	6.8	8.8
<b>6a</b>	-- (h)	-- (i, j)	1685	0.07 (m, 4), 0.93 (m, 4),	C <sub>12</sub> H <sub>13</sub> NO	77.0	7.0	7.5
				1.77 (m, 1), 7.29 (m, 3), 8.44 (m, 1) (k)		77.0	7.0	7.5
<b>6b</b>	-- (h)	-- (i, l)	1669	0.49 (m, 4), 1.31 (m, 5),	C <sub>12</sub> H <sub>13</sub> NO	77.0	7.0	7.5
				7.18 (m, 1), 7.92 (m, 1), 8.47 (m, 1), 8.93 (m, 1)		76.8	6.9	7.4
<b>6c</b>	-- (h)	-- (i, m)	1695	0.16 (m, 4), 1.00 (m, 5),	C <sub>12</sub> H <sub>13</sub> NO	77.0	7.0	7.5
				7.53 (m, 2), 8.59 (m, 2) (k)		76.7	6.7	7.2

(a) Carbon tetrachloride solution. (b) Carbon tetrachloride solution with tetramethylsilane as an internal standard unless otherwise noted. (c) Recrystallized from petroleum ether (30-60°). (d) Lit. (1): m.p. 36-37°. (e) Deuteriochloroform solution with tetramethylsilane as internal standard. (f) Recrystallized from cyclohexane. (g) Lit. (10): m.p. 63-66°. (h) No valid yield data obtainable. (i) Isolated by glpc (column temperature of 150°) of crude distillate. (j) Crude distillate fraction: b.p. 52-93° (0.04 mm.). (k) Carbon tetrachloride solution in a spherical microcell with dichloromethane as an external standard. (l) Crude distillate fraction: b.p. 72-115° (0.23 mm.). (m) Crude distillate fraction: b.p. 53-89° (0.03 mm.).

potassium amide (21,22) and lithium diisopropylamide (22) were examined. The former gave only a trace yield (≈4%) of **2b**, while the latter proved more successful and under optimum conditions gave **2b** in 23% yield.

## EXPERIMENTAL

The properties and identifying spectral data for all compounds are given in Table I. The ir spectra were obtained on a Perkin Elmer 621 spectrophotometer. All nmr spectra were obtained on a Varian A60A spectrometer. Melting points (Thomas-Hoover apparatus) and boiling points are uncorrected. Preparative gas chromatography (glpc) was carried out using a Bendix model 2300 gas chromatograph with 5 ft. x 0.25 in. copper columns packed with 5% SE-30 on Chromosorb G-HP (80-100 mesh) with helium carrier gas at 60 ml./min. flow rate.

General Procedure for Synthesis of Cyclopropyl Pyridyl Ketones (**1a-c**, **6a-c**).

Cyclopropyllithium (**9**).

To 10.9 g. (1.58 mole) of lithium wire in small pieces (3 mm. x 1 cm.) in 400 ml. of anhydrous ether under argon was added with rapid stirring 90.6 g. (0.75 mole) of cyclopropyl bromide (**23**) in 100 ml. of anhydrous ether. The addition rate was such as to maintain a gentle reflux and addition required ca. 3 hours. The resulting orange-brown mixture containing a small amount of unreacted lithium was stirred at room temperature for 4 hours, packed in dry-ice and allowed to stand overnight.

Ketones.

A 2 l. three-neck flask, which was equipped with mechanical stirrer, low temperature thermometer and a 250 ml. addition funnel with metering valve, pressure equalizing sidearm and polyethylene extension of the drip tip to allow addition directly onto the reaction solution, was charged with 300 ml. of anhydrous ether and cooled to -70°. To the well-stirred ether was added 52 g. (0.5 mole) of the appropriate cyanopyridine (**5a-c**) in 300 ml. (**24**) of anhydrous ether keeping the temperature below -65°. The resulting mixture was placed under argon and the cyclopropyllithium solution (previously warmed to room temperature) was

added (25) with rapid stirring while keeping the temperature below  $-65^{\circ}$ . The reaction mixture was then stirred at about  $-70^{\circ}$  for 2 hours, the cooling bath removed and stirring continued for 2 hours while the reaction warmed to near room temperature. Aqueous ammonium chloride (30%, 125 ml.) followed by 200 ml. of 6 *N* hydrochloric acid were added (pH 1) while keeping the mixture's temperature between  $10-25^{\circ}$ . The ether layer was separated and washed with 10% hydrochloric acid (2 x 50 ml.). After standing for 0.5 hour at room temperature, the combined aqueous layers were cooled and basified to pH 10 with 150 ml. of 50% sodium hydroxide. The resulting mixture was extracted with ether. The ether was dried (sodium sulfate) and removed under reduced pressure to give a dark oil which on distillation afforded **1a-c** and a higher boiling fraction which was a mixture of **1a-c** and **6a-c**.

#### Cyclopropyl 2-Picolyl Ketone (**2a**).

To a stirred solution of 500 ml. (1.0 mole) of 2.0 *M* phenyllithium in benzene/ether (70:30) and 250 ml. of anhydrous ether under argon was added 93.13 g. (1.0 mole) of 2-picoline (**9a**) in 200 ml. of anhydrous ether over 0.5 hour. The resulting solution was heated under reflux for 0.5 hour and cooled to room temperature. Cyclopropyl cyanide (33.55 g., 0.5 mole) in 150 ml. of anhydrous ether was added over a 0.5 hour period with rapid stirring. The resulting solution was heated under reflux for 0.5 hour, cooled and 200 ml. of a 30% aqueous ammonium chloride solution was added keeping the temperature below  $15^{\circ}$ . The reaction mixture was then acidified with 200 ml. of 12 *N* hydrochloric acid to pH 1, keeping the temperature below  $25^{\circ}$ . The organic layer was separated, washed with 10% hydrochloric acid (2 x 50 ml.) and discarded. The combined aqueous layers were washed with 100 ml. of ether, stirred for 0.5 hour at room temperature, cooled and basified to pH 10 with 150 ml. of 50% aqueous sodium hydroxide. The resulting mixture was extracted with ether and the ether was dried (sodium sulfate). The ether solution was concentrated under reduced pressure to give an oil which on distillation gave 69.5 g. (86%) of **2a**: b.p.  $80-83^{\circ}$  (0.5 mm.).

#### Cyclopropyl 3-Picolyl Ketone (**2b**).

To 101 g. (1.0 mole) of diisopropylamine in 700 ml. of anhydrous ether under argon was added with cooling and stirring 455 ml. (1.0 mole) of 2.2 *M* *n*-butyllithium in hexane over 1 hour. The resulting solution was stirred at room temperature for 2 hours and 93.13 g. (1.0 mole) of 3-picoline (**9b**) in 200 ml. of anhydrous ether was added over 2 hours. The reaction solution was stirred overnight. A solution of 33.55 g. (0.5 mole) of cyclopropyl cyanide in 200 ml. of anhydrous ether was then added over 0.5 hour with rapid stirring followed by stirring for 2 hours. Hydrolysis and product isolation were carried out as in the synthesis of **2a** to give a dark oil which on distillation gave 18.7 g. (23%) of **2b**: b.p.  $99-101^{\circ}$  (0.09 mm.).

#### Cyclopropyl 4-Picolyl Ketone (**2c**).

To 88.2 g. (1.05 mole) of thiophene in 1 l. of anhydrous ether at  $0^{\circ}$  under argon was added with stirring over a 0.75 hour period 455 ml. (1.0 mole) of 2.2 *M* *n*-butyllithium in hexane (26). The resulting solution of 2-thienyllithium was stirred for 2.5 hours at room temperature and then 93.13 g. (1.0 mole) of 4-picoline (**9c**) in 100 ml. of anhydrous ether was added over 1 hour. The reaction mixture was stirred overnight. A solution of 33.55 g. (0.5 mole) of cyclopropyl cyanide in 100 ml. of anhydrous ether was then added over a 0.75 hour period with rapid stirring. The

reaction mixture was stirred for 3 hours at room temperature and heated under reflux for 0.5 hour. Hydrolysis and product isolation were carried out as in the synthesis of **2a** to give a dark oil which on distillation gave 49.07 g. of crude **2c** (b.p.  $81-85^{\circ}$ , 0.4 mm.) which partially solidified. Recrystallization from hexane afforded 31.1 g. (38%) of **2c**.

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#### REFERENCES

- (1) F. J. McCarty, C. H. Tilford, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **79**, 472 (1957).
- (2) Breuer (3) reported **1b** but did not describe a method or give physical data.
- (3) E. Breuer and D. Melumad, *Tetrahedron Letters*, 3595 (1969).
- (4) R. V. Stevens, M. C. Ellis and M. P. Wentland, *J. Am. Chem. Soc.*, **90**, 5576 (1968).
- (5) H. L. Yale in "Pyridine and Its Derivatives," Volume XIV, Part II, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, pp. 422-3 and references cited therein.
- (6) A modified version of this synthesis for the preparation of cyclopropyl 3-pyridyl ketone (carbonyl- $^{14}\text{C}$ ) has previously been reported in our laboratories by R. A. Comes, M. T. Core, M. D. Edmonds, W. B. Edwards, III and R. W. Jenkins, in *J. Label. Compounds*, **9**, 253 (1973).
- (7) H. Hart, *Chem. Ind. (London)*, 1014 (1956).
- (8) H. M. Walborsky, G. E. Niznik and M. P. Periasamy, *Tetrahedron Letters*, 4965 (1971); R. Magid and S. E. Wilson, *ibid.*, 4925 (1969); D. T. Longone and W. D. Wright, *ibid.*, 2859 (1969); H. Hart and R. A. Cipriani, *J. Am. Chem. Soc.*, **84**, 3697 (1962).
- (9) D. Seyferth and H. M. Cohen, *Inorg. Chem.*, **2**, 625 (1963).
- (10) B. Brust, R. I. Fryer and L. H. Sternbach, U. S. Patent 3,371,096 (1968); *Chem. Abstr.*, **65**, PC 544e (1966).
- (11) N. N. Goldberg, L. B. Barkley and R. Levine, *J. Am. Chem. Soc.*, **73**, 4302 (1951).
- (12) A 1:1:0.5 mole ratio of **9a**, phenyllithium and cyclopropyl cyanide was employed (11).
- (13) C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956).
- (14) J. P. Wibaut and J. W. Hey, *Rec. Trav. Chem.*, **72**, 513 (1953).
- (15) C. G. Screttas, J. F. Estham and C. W. Kamienski, *Chimia*, **24**, 109 (1970); C. G. Screttas, U. S. Patent 3,691,174 (1972).
- (16) When benzophenone was used in lieu of cyclopropyl cyanide in a repeat of the original work (15), a 90% yield of 1,1-diphenyl-2-(4-pyridyl)ethanol was obtained.
- (17) Available from Aldrich Chemical Company, Inc.
- (18) Structure proof obtained by comparison with independently synthesized (from **10** and cyclopropyl cyanide) sample: b.p.  $59-60^{\circ}$  (0.06 mm.); ir (carbon tetrachloride): 3295 (NH) and  $1610\text{ cm}^{-1}$  (C=N); nmr (deuteriochloroform):  $\delta$  0.95 (m, 4, cyclopropyl methylene), 2.15 (m, 1, cyclopropyl methine), 7.18 (m, 1, thiophene 4H), 7.56 (m, 2, thiophene, 3 and 5H), 8.74 (broad s, 1, NH). *Anal. Calcd.* for  $\text{C}_8\text{H}_9\text{NS}$ : C, 63.5; H,

6.0; N, 9.3; S, 21.2. Found: C, 63.4; H, 6.0; N, 9.1; S, 21.4.

(19) While it initially appeared that the hydrolysis rate of **11** to the corresponding ketone was unusually slow, a preliminary determination of the rate showed it to be of the order of  $10^{-3}$  min.<sup>-1</sup> at 25°. This rate is in line with what would be expected (20) and implied that the rate of hydrolysis for **4a-c** and the cyclopropyl picolyl ketimines was unusually fast. This is currently being investigated.

(20) J. B. Cloke, L. H. Baer, J. M. Robbins and G. E. Smith, *J. Am. Chem. Soc.*, **67**, 2155 (1945); J. B. Culbertson and L. Hines, *Proc. Iowa Acad. Sci.*, **41**, 172 (1934); *Chem. Abstr.*, **29**, 3582<sup>8</sup> (1935).

(21) A. D. Miller and R. Levine, *J. Org. Chem.*, **22**, 168 (1957).

(22) A. D. Miller, C. Osuch, N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

(23) Supplied by Columbia Organic Chemical Company, Inc., Columbia, South Carolina.

(24) Because of the low solubility of **5c** in ether, 800 ml. was required.

(25) Transfer of the cyclopropyllithium solution to the addition funnel was carried out under argon using syringe needles and vacuum.

(26) V. Ramanathan and R. Levine, *J. Org. Chem.*, **27**, 1667 (1962).