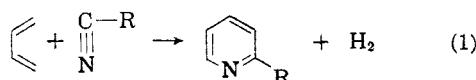# Gas Phase Synthesis of 2-Trifluoromethyl-pyridines[1]

GEORGE J. JANZ AND MICHAEL A. DE CRESCENTE

The gas phase cyclization of nitriles with dienes at moderately high temperatures, with loss of hydrogen to yield substituted pyridines:

$$\text{(structure)} + \overset{\text{C}-\text{R}}{\underset{\text{N}}{|||}} \rightarrow \text{(pyridine structure)} + \text{H}_2 \quad (1)$$

has been reported by Janz and co-workers.[2] The reaction has been found to be an example of the Diels-Alder type synthesis, in which the (C≡N) group exhibits dienophilic properties, and in which the dihydro-cyclic adduct loses hydrogen spontaneously at the elevated temperatures to form the pyridinic products. Trifluoroacetonitrile, like cyanogen, cyclizes with butadiene at 350°–520° without the aid of a catalyst.[2e] The present communication describes the results of some studies at relatively long reaction periods, extending the experiments with trifluoroacetonitrile to pentadiene and isoprene, as well as butadiene.

EXPERIMENTAL

Chemicals. Trifluoroacetonitrile (Columbia Organic) and butadiene (Matheson) were purified by low temperature distillation and degassed under vacuum prior to use. *Isoprene* (Matheson) was redistilled at atmospheric pressure just prior to use. The *pentadiene* was a research sample from Phillips Petroleum containing 91% of predominantly cis-1,3-pentadiene, and 9% of cyclopentenes and hexenes. Prior to an experiment, it was also redistilled at atmospheric pressure.

Apparatus and procedure: The continuous flow reaction system was similar to that used previously,[2e] but with a 5.38-l. flask as the reaction zone to achieve longer contact times at lower flow rates. The reaction conditions, material balances, and yields are summarized in Table I. The loss of material in the experiments with butadiene and isoprene is attributed to volatilization in the final weighings rather than pyrolysis, and the yields were corrected accordingly. These could undoubtedly be minimized with improved low temperature gas transfer techniques. After each flow experiment was completed, the product separation was achieved by low temperature fractionation for the diene and nitrile recoveries, and the pyridinic compound, by fractional distillation through a Podbielniak semi-micro analyzer. The physical properties found for the pyridinic products are given in Table II. The trifluoromethylpyridines were found to be essentially non-basic, *i.e.* attempts to prepare picrate derivatives were unsuccessful, and they could not be titrated as bases in the conventional manner.

(1) Part XII in the series, The Reaction of Cyanogen and Related Nitriles With 1,3-Dienes.

(2) (a) G. J. Janz, R. G. Ascah, and A. G. Keenan, *Can. J. Res.* B25, 272, 283 (1947); (b) G. J. Janz and S. C. Wait, Jr., *J. Am. Chem. Soc.*, 76, 6377 (1954); (c) G. J. Janz and W. J. McCulloch, *J. Am. Chem. Soc.*, 77, 3014, 3143 (1955); (d) G. J. Janz, J. M. S. Jarrie, and W. E. Fitzgerald, *J. Am. Chem. Soc.*, 78, 978 (1956); (e) G. J. Janz and J. M. S. Jarrie, *J. Phys. Chem.*, 60, 1430 (1956).

TABLE I

REACTION CONDITIONS, MATERIAL BALANCE AND YIELDS

	Butadiene	Pentadiene	Isoprene
Reaction Conditions			
Contact time (sec.)	2490	1568	1760
Total time (hr.)	2.88	8.71	7.17
Temp. (°C.)	400	401	400
Ratio, RCN/diene (mole)	0.67	0.49	0.52
Diene input (moles)	0.244	1.303	0.95
Nitrile input (mole)	0.162	0.637	0.495
Material balance (wt. %)	91	99	95
Conversions			
Nitrile conv. (mole)	0.093	0.356	0.343
Diene conv. (mole)	0.171	0.629	0.629
Yields of Pyridinic Product			
Pyridinic prod. (mole)	0.094	0.350	0.339
Yield (%, diene)	55	56	54
Yield (%, CF₃CN)	100	98	100

TABLE II

PHYSICAL PROPERTIES OF TRIFLUOROMETHYLPYRIDINES

Diene Pyridine-	Butadiene 2-Trifluoro-methyl-	Pentadiene 6-Methyl-2-trifluoro-methyl-	Isoprene 4-Methyl-2-trifluoro-methyl-
n_D^{25}	1.4155	1.4262	1.4380
B.p. (°C.)	143 (745 mm.)	153 (756 mm.)	171 (760 mm.)
M.p. (°C.)	...	12.5	...
Infrared spectra	(Ref. 2)	This work	This work

A Perkin-Elmer model 21 double-beam recording spectrometer equipped with NaCl and LiF optics was used to obtain the spectra for these pyridines as liquids.

2-Trifluoromethylpyridine. The infrared spectrum, vibrational assignment of the ring fundamentals and CF₃ modes, and product identification have been described in an earlier communication,[2d] and need no further comment.

6-Methyl-2-trifluoromethylpyridine. Infrared frequencies (cm.⁻¹) and intensities:[3] 3477 (m); 3027 (w), 2488 (w), 2262 (w), 2124 (v.w.), 1987 (s), 1902 (s), 1881 (v.w.), 1779 (v.w.), 1748 (w), 1672 (v.w.), 1608 (v.s.), 1581 (v.w.), 1466 (v.s.), 1426 (v.s.), 1378 (v.s.), 1338 (v.s.), 1290 (s), 1261 (v.s.), 1245 (v.s.), 1183 (s), 1171 (s), 1157 (s), 1139 (m.s.), 1103 (s), 1093 (s), 1075 (w), 1042 (s), 999 (v.s.), 990 (w), 911 (s), 878 (v.s.), 847 (v.w.), 805 (v.s.), 746 (v.s.), 658 (s); LiF resolution: 3022 (s), 3019 (s), 2956 (s), 2930 (s), 2872 (s). Inspection of the generalized cyclization-dehydrogenation reaction (1) leaves little doubt as to the identity of this pyridinic product since 6-methyl-2-trifluoromethylpyridine is the only isomeric pyridine feasible with pentadiene and CF₃CN as reactants. The vibrational assignment (below) confirms the identity of this product through the empirical recognition of these structural units.

Anal. Calculated for C₇H₆NF₃: N, 8.69. Found; N, 9.02.

4-Methyl-2-trifluoromethylpyridine. Infrared frequencies (cm.⁻¹) and intensities: 3442 (m), 3017 (w), 2950 (v.s.), 2495 (w), 2197 (v.w.), 2092 (w), 1989 (m), 1895 (m), 1741

(3) Filed with the Catalog of Infrared Spectral Data, A.P.I. Project 44, Petroleum Research Laboratory, Carnegie Institute of Technology.

(m), 1674 (v.w.), 1614 (v.s.), 1586 (m), 1570 (w), 1509 (w), 1493 (w), 1441 (w), 1421 (v.s.), 1379 (s), 1327 (v.s.), 1299 (w), 1250 (s), 1209 (s), 1176 (s), 1135 (s), 1117 (s), 1088 (s), 1044 (s), 1031 (s), 998 (v.s.), 977 (w), 948 (v.w.), 896 (s), 876 (v.s.), 836 (v.s.), 800 (v.w.), 757 (v.s.), 749 (s), 719 (s), 686 (v.s.), 654 (m), 645 (s); LiF resolution: 3702 (s), 3062 (s), 3027 (s), 2971 (s), 2932 (s), 2873 (s).

Two trifluoromethylpyridines, *i.e.* the 4-methyl-and 5-methyl-isomers, may be conceived as products in this reaction (1) with isoprene and CF_3CN as reactants. The identity of the product as the 4-methyl-2-trifluoromethyl isomer rather than the 5-methyl-2-trifluoromethyl isomer or a mixture of the two is in accord with previous syntheses using isoprene and CH_3CN, C_6H_5CN, and $(CN)_2$ as nitriles, respectively.[2c] The 4-methyl-substituted pyridine was the only product found in each case. Comparison of the observed boiling point (171°, Table I) with the values predicted for 4-methyl-2-trifluoromethyl pyridine (172°) and 5-methyl-2-trifluoromethylpyridine (176°), and the vibrational assignment (below) leave little doubt as to the product identity.

The values for the boiling points were estimated from those of 2-trifluoromethylpyridine (Table I, 143°), 2-picoline[4] (128°), 2,3-lutidene[5] (161°), and 2,4-lutidene (157°), assuming that the non-bonded interactions account for the additive properties[6] in the isomeric trifluoromethylpyridines as in the lutidene series.

Anal. Calculated for $C_7H_6NF_3$: N, 8.69. Found; N, 8.40.

Vibrational assignment: The infrared absorption frequencies generally used to characterize pyridines are those suggested by Cannon and Sutherland:[7] 3020, 1600 to 1590, 1500 (s) or lower, near 1200 (s), 1100 to 1000 (s), 900 to 650—two strong bands. The observed frequencies at 3027, 1600, 1466, 1245, 1103, 878, 805, and 3017, 1596, 1421, 1209, 1117, 896, 757 for the 6-methyl-and the 4-methyl-2-trifluoromethyl pyridines respectively, are in accord with the pyridinic ring assignments. The corresponding vibrations in 2-trifluoromethylpyridine were 3040, 1596, 1445, 1250, 1100, 795, and 745. For the CF_3 group Randle and Whiffen[8] reported the mean values for the C—F stretching modes of aromatic trifluoromethyl compounds to be: 1321 ± 9, 1179 ± 7, and 1140 ± 9 (cm.⁻¹). Inspection of the observed spectra reveals these characteristic absorptions at 1338, 1183, 1139 and 1327, 1176, 1135 for the 6-methyl- and the 4-methyl-substituted pyridines, respectively. An investigation[9] of a series of benzotrifluorides resulted in the assignment of a CF_2 deformation frequency at 658–665 cm.⁻¹ The 6-methyl and the 4-methyl compounds show strong absorptions at 658 and 686 (cm.⁻¹), respectively. Symmetrical deformation frequencies occur at 760 in CF_3Br and 741 (cm.⁻¹) in CF_3I. Strong absorption frequencies in the spectra of the 6-methyl and the 4-methyl substituted pyridines occur at 746 and 749 cm.⁻¹, respectively. The C—H stretching frequencies of the CH_3 group in a series of hydrocarbons assigned by Fox and Martin[10] in the region of 3000 cm.⁻¹ (LiF resolution) are 2962, 2934, 2912, and 2872 (cm.⁻¹). 6-Methyl-2-trifluoromethylpyridine has bands at 2956, 2930, and 2872; 4-methyl-2-trifluoromethylpyridine, at 2971, 2932, and 2873 (cm.⁻¹).

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(5) T. Eguchi, *Bull. Chem. Soc. Japan*, **3**, 227 (1928).

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(8) R. R. Randle and D. M. Whiffen, *J. Chem. Soc.*, 1311 (1955).

(9) D. C. Smith, J. R. Nielsen, L. H. Berryman, H. H. Claassen, and R. L. Hudson, *Spectroscopic Properties of Fluorocarbons and Fluorinated Hydrocarbons*, NRL Report 3567 (1949).

(10) J. J. Fox and A. E. Martin, *Proc. Roy. Soc.*, **A175**, 208, 234 (1940).

DISCUSSION

The high reactivity in this Diels-Alder synthesis of trifluoroacetonitrile undoubtedly may be attributed to the polarization of the (C≡N) link by the proximity of the CF_3 group with its strong electrophilic properties. In preliminary experiments with trifluoroacetonitrile alone, this compound proved thermally very stable, showing no trace of pyrolysis or self-polymerization in the region 350°–500°. Inspection of the results in Table I shows clearly that the reacted nitrile may be accounted for entirely by the Diels-Alder process, *i.e.* the yield of pyridinic product is 100 mole percent, within experimental limits of accuracy, based on trifluoroacetonitrile.

The lower yields, based on the dienes, may be attributed to the fact that two different dienophilic groups, *i.e.* the C=C and the C≡N groups, are competing for the diene. Thus for butadiene, 3-vinylcyclohexene as well as 2-trifluoromethylpyridine was confirmed in the product analyses. No effort was made in the present phase of the work to estimate such products quantitatively. Inspection of the data in Table 1 shows that 44–46 mole percent of the diene that has been converted per pass may be accounted for in this manner. With CF_3CN in large excess, the effect of this competing process would undoubtedly be minimized.

The results in Table I are of further interest to ascertain whether kinetic or thermodynamic control is operative at these long reaction times. In the study of gaseous reactions in continuous flow systems, providing the operating conditions are comparable, the concept of space-time-yield (S.T.-Y.) offers a direct insight[11] on kinetic control since it is directly proportional to the rate constant. From the definition of S.T.Y., *i.e.* moles of product/unit time/unit reaction volume, it follows in the present case, that:

$$\text{S.T.Y.} = \left(\frac{\text{moles pyridinic product}}{\text{volume of reaction vessel}}\right) = k_2\left(\frac{N_DN_T}{V_0}\right) \quad (2)$$

where N_D, N_T are the moles of diene and nitrile, V_0 is the velocity of flow of the entering mixture, and k_2 the rate constant. The relation strictly applies only at low conversions, but has been used as a first approximation to calculate the space-time-yields in the present instance.

Diene	Butadiene	Pentadiene	Isoprene
S.T.Y.[a]	6.1×10^{-4}	7.8×10^{-4}	8.8×10^{-4}

[a] Units, moles/hr./100 cc. reaction zone.

It follows from Equation 2 that the values of the space-time-yield should directly reflect the relative reactivities of the three dienes if the reactions are subject to kinetic control. The values of the S.T.Y. (above) are all the same order of magnitude, no significance being attributable to the small dif-

(11) G. J. Janz and S. C. Wait, Jr., *J. Chem. Phys.*, **23**, 1550 (1955).

ference to the variation in the pre-exponential factor. The closely similar diene conversions (Table I) are also in accord with the possibility that these yields reflect equilibrium rather than rate values.

By the method of statistical thermodynamic functions, the free energy change for the butadiene-trifluoroacetonitrile reaction was calculated. Using the precise values[12,13] for butadiene, hydrogen, and trifluoroacetonitrile, and the methods[14] of group equations and group increments to estimate the functions for trifluoromethylpyridine and the heats of formation for CF_3CN and the latter, it was found that ΔF° was negative over the entire temperature range $300°-1000°$ K., being -9 kcal./mole at the upper limit. It is sufficient for the present discussion to refer only to the result at $400°$. The standard free energy change, and the equilibrium S.T.Y. calculated from the well known equation:

$$\Delta F^\circ = -RT \ln K_p \qquad (3)$$

at $400°$ were thus found to be -14 kcal./mole and 13×10^{-4} moles/hr./100 cc. reaction volume.

Comparison of the thermodynamically predicted value with the experimental S.T.Y., 6.1×10^{-4}, confirms that the present yields should be recognized as equilibrium yields, i.e. that thermodynamic control rather than kinetic control operates. It should be noted that the preceding results should be interpreted only qualitatively rather than giving a quantitative estimate of the nearness to equilibrium conditions in these experiments.

Extension of these studies is in progress at very short reaction times as well as very long periods, to evaluate the relative reactivities of the dienes and the reaction equilibria in the homogeneous gas phase at moderately high temperatures.

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## Methyl Desoxypodophyllate and Its Methyl Ether

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In a previous paper from this laboratory,[1] it was shown that anthricin (isolated by Noguchi and

Kawanami[2] from *Anthriscus sylvestris* Hoffm.), hernandion (isolated by Hata[3] from *Hernandia ovigera* L.), and silicicolin [isolated by Hartwell, Johnson, Fitzgerald, and Belkin[4] from *Juniperus silicicola* (Small) Bailey] are all identical with desoxypodophyllotoxin (I),[5,6] a compound also obtained[7] from *Podophyllum peltatum* L. Base-catalyzed epimerization of I (at C_3) produces the *cis*-(2:3)-*trans*-(3:4) desoxypicropodophyllin (II),[5,6] which is identical[1] with isohernandion,[3] with silicicolin-B,[5] and also with cicutin (isolated by Marion[8] from *Cicuta maculata* L.[9]). Both I and II are saponified to the same hydroxy acid, desoxypodophyllic acid (IIIa), which in turn is lactonized to II.[5] Noguchi's isoanthricin[2] was probably[1] a mixture of this acid with some II.

I

II
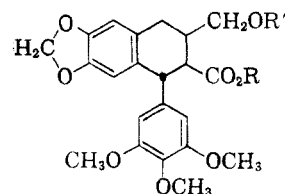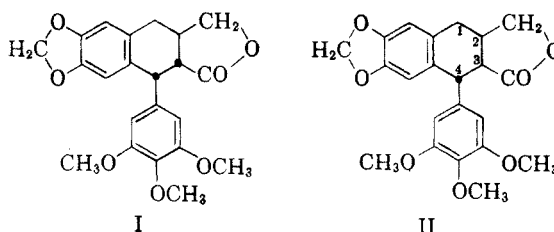
IIIa: R = R' = H
IIIb: R = CH₃; R' = H
IIIc: R = H; R' = CH₃
IIId: R = R' = CH₃

In view of the identity of the various lactones with I or II, it is difficult to understand certain apparent discrepancies with regard to their reactions. Thus, Noguchi and Kawanami[2] reported that treat-

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(9) Cicutin is probably[1] an artifact, produced by epimerization of desoxypodophyllotoxin during its isolation, which included treatment with methanolic sodium hydroxide.