New Synthetic Routes to 3-, 5-, and 6-Aryl-2-chloropyridines

Robert Church, Ronald Trust, J. Donald Albright, and Dennis W. Powell*

American Cyanamid Company, Medical Research Division, Lederle Laboratories, Pearl River, New York 10965

Received November 21, 1994[⊗]

The efficient synthesis of 3-, 5-, and 6-aryl-2-chloropyridines via the facile preparation of 5-(dimethyamino)aryl-substituted pentadienyl nitriles and cyclization with hydrochloric acid is described. This approach allows for the introduction of other electron-withdrawing substituents on the pyridine ring as well as the preparation of the desired unsubstituted arylpyridines. Some differences in the rates of cyclization of the pentadienyl nitriles as well as the yields of chloropyridines were observed that depended on the position and degree of substitution in the aryl substituent. The arylpentadienyl nitriles **5** and **6** could also be converted directly into the corresponding 2-aminopyridines.

Introduction

Our initial interest in aryl-substituted 1,2,4-triazolo-[4,3-*a*]pyridines **1** stemmed from the anxiolytic activity observed in a series of 6-aryl-1,2,4-triazolo[4,3-*a*]pyridazines **2**.[1] In particular the potent activity (pentylenetetrazole antagonism, thirsty rat conflict, and binding to benzodiazepine receptor sites) of triazolopyridazine **2a** prompted us to investigate the synthesis of the structurally related aryl-1,2,4-triazolo[4,3-*a*]pyridines **1**[2] (Figure 1).

The key intermediates in the preparation of **1** are aryl-2-halopyridines **3** which can be readily prepared from the corresponding aryl-2-pyridones **4** (Figure 1). Methods for the synthesis of 3-,[3] 4-,[4] 5-,[2] and 6-aryl-2-pyridones[4] have been reported; however, these syntheses either require long multistep sequences or were not applicable for the preparation of unsubstituted aryl-2-halopyridines which we sought.[4] We wish to report our initial efforts to prepare 5-aryl-2-chloropyridines via 5-aryl-2-pyridones as well as the more efficient syntheses of 3-, 5-, and 6-aryl-2-chloropyridines based on the preparation and ring closure of appropriately substituted 5-(*N*,*N*-dimethylamino)-2,4-pentadienenitriles **5**–**7** (Figure 2).

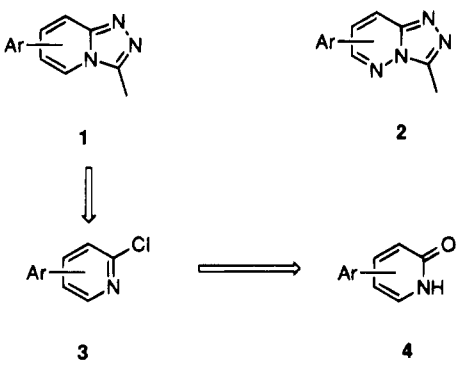


Figure 1.

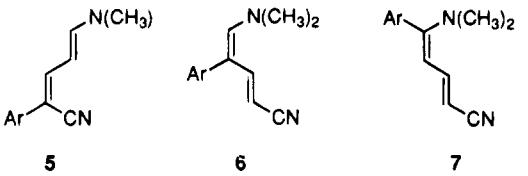


Figure 2.

Results

Bryson *et al.* reported that ethyl 2-cyano-5-(dimethylamino)-2,4-pentadienoate (**8a**) ($R_1 = R_2 = H$) was cyclized in hot acetic acid with hydrobromic acid to afford the unsubstituted ethyl bromonicotinic acid (**9a**) ($R_1 = R_2 =$ H) in excellent yield[5] (Figure 3). Bryson proposed that the cyclization proceeded through initial addition of hydrobromic acid across the nitrile followed by a Michael addition–elimination to the ester. Ponticello *et al.* showed that substituted ethyl 2-cyano-5-(dimethylamino)-2,4-pentadienoates (**8b**) ($R_1 = CH_3$, H; $R_2 = CH_3$,H) also cyclized but in modest yields.[6] We were interested in modifying this strategy to prepare **1**. It was clear from

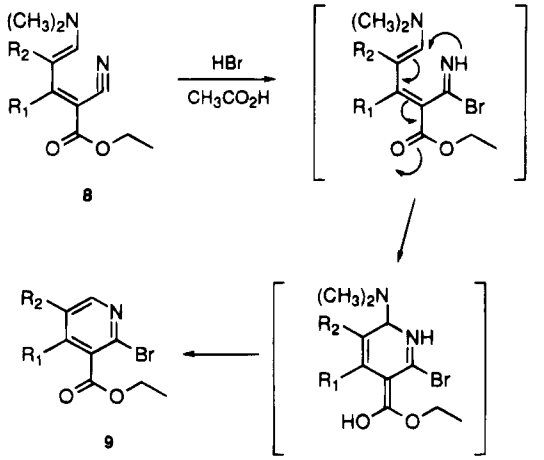


Figure 3.

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1995.

(1) Albright, J. D.; Moran D. B.; Wright, W. B., Jr.; Collins, J. B.; Beer, B.; Lippa, A. S.; Greenblatt, E. N. *J. Med. Chem.* **1981**, *24*, 592. Albright, J. D.; Powell, D. W.; Dusza, J. P. U.S. Patent 4 654 343, 1987. Albright, J. D.; Powell, D. W.; Dusza, J. P. U.S. Patent 4 767 765, 1988. Albright, J. D.; Powell, D. W.; Dusza, J. P. U.S. Patent 4 892 873, 1990; *Chem. Abstr.* **1987**, *107*, 39844.

(2) Albright, J. D.; Trust, R. J. U.S. Patent 4,242,515, 1980; *Chem. Abstr.* **1981**, *94*, 139815.

(3) Elroy, F.; Desyckere, A. *Chim. Ther.* **1970**, 416.

(4) Thesing, J.; Muller, A. *Chem. Ber.* **1957**, 711.

(5) Bryson, T. A.; Wisowatz, J. C.; Dunlap, R. B.; Fischer, R. R.; Ellis, P. D. *J. Org. Chem.* **1974**, *39*, 3436. Bryson, T. A.; Donelson, D. M.; Dunlap, R. B.; Fischer, R. R.; Ellis, P. D. *Ibid.* **1976**, *41*, 2066.

(6) Ponticello, G. S.; Hartmann, R. D.; Lumma, W. C., Jr.; Balwin, J. J. *J. Org. Chem.* **1979**, *44*, 3080.

0022-3263/95/1960-3750$09.00/0

Scheme 1

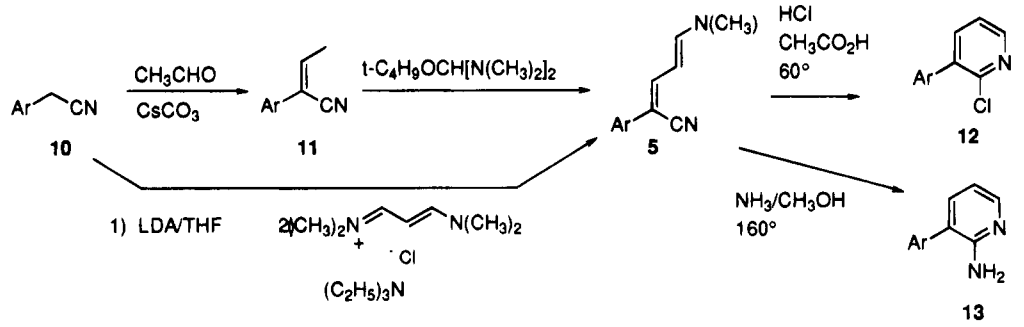


Table 1. Arylacetonitriles[a]

compd	Ar	R	mp/bp, °C	procedure	recrystallization solvent	% yield[a]
11a	3-pyridinyl	CH_3	46.5–47.5	A	hexane	59
11b	3-CF_3-Ph	CH_3	83–87/0.4 mmHg	A		57
11c	3-CH_3O-Ph	CH_3	oil	A		38
5a	3-pyridinyl	$CHCHN(CH_3)_2$	145–147	B	CH_2Cl_2–hexane	94
5b	3-CF_3-Ph	$CHCHN(CH_3)_2$	117–118	B	CH_2Cl_2–hexane	66[b], 55[c]
5c	3-CH_3O-Ph	$CHCHN(CH_3)_2$	101.5–103.5	B	CH_2Cl_2–hexane	81
5d	phenyl	$CHCHN(CH_3)_2$	105–106.5	B	CH_2Cl_2–hexane	60[d]

[a] Satisfactory analytical data (±0.4% for C,H,N, etc.) were reported for all new compounds. [b] Yield from **11b**. [c] Yield from 3-(trifluoromethyl)phenylacetonitrile; see experimental. [d] Prepared from α-ethylidene-3-phenylacetonitrile.[8]

the biological structure–activity information obtained from the 6-aryltriazolopyridazines **2**, that the introduction of additional substituents on the pyridazine ring in **2** was deleterious to biological activity,[1] and therefore an efficient synthesis of **1** would avoid the introduction and removal of the ethyl ester. However, it was unclear whether the ethyl ester was necessary for efficient cyclization or whether other electron-withdrawing groups could effectively substitute for the ethyl ester. In addition we were interested in knowing whether or not electron-donating or -withdrawing phenyl groups in various positions along the diene chain would affect the cyclization.

3-Aryl-2-chloropyridines. While several examples of syntheses of **5** appear in the literature,[7] we decided to prepare **5** by the following two methods for the sake of convenience. Arylacetonitriles **10** were condensed with acetaldehyde in absolute ethanol with a catalytic amount of cesium carbonate to afford α,β-unsaturated nitriles **11** in 50–80% yield (Scheme 1, Table 1). Sodium ethoxide,[8] sodium bicarbonate, or potassium carbonate in ethanol gave much lower yields of **11**. Arylacetonitriles with electron-donating aryl groups tended to require much longer reaction times. Formylation of **11** was performed with *tert*-butoxybis(dimethylamino)methane in tetrahydrofuran at 20 °C. Alternatively, **5** could be prepared by a modification of the Jutz[7] procedure by using lithium diisopropylamide (LDA) and 1,1,5,5,-tetramethyl-1,5-diazapentadienium chloride[9] (Table 1). This latter method affords moderate yields of **5** directly and suffers only from the necessity of having to prepare the water sensitive iminium salt.[10]

Cyclization of **5** to 3-aryl-2-chloropyridines **12** (Table 2) was carried out under modified literature conditions. It was found that dry hydrogen chloride (*ca.* 4 equiv) in glacial acetic acid at 60 °C for 2–3 h is superior to hydrogen bromide in acetic acid[5,6] with respect to yields obtained and ease of handling. In addition, for subsequent reactions, the 2-chloropyridines appeared to react better with hydrazine and other amine nucleophiles than the corresponding bromides. Cyclization of **5** at 20 °C with hydrogen chloride in acetic acid led to poor yields of **12**. Of note is the significant difference in cyclization yields among dienes bearing electron rich or electron poor phenyl groups. In addition, the dienes **5** could be converted directly to 2-aminopyridines **13** (Table 2) by heating at 160 °C with ammonia in methanol.[11]

5-Aryl-2-chloropyridines. Initially,[2] 5-aryl-2-chloropyridines **20** were prepared via the synthetic route depicted in Scheme 2. Condensation of 2-aryl-3-(dimethylamino)-2-propenals **16** with cyanoacetamide is reported[12] to give 3-cyano-5-aryl-2-pyridones 17. The 2-aryl-3-(dimethylamino)-2-propenals **16** (Table 3) were synthesized by Vilsmeier diformylation/decarboxylation of arylacetic acids according to the general procedure of Arnold.[13] The propenal **16** was condensed with several three-carbon fragments such as malonamide, ethyl malonamide, or cyanoacetamide. In a limited study, condensations with cyanoacetamide gave the best yields of cyclized products (see Table 3).

(7) (a) Bredereck, H.; Effenberger, F.; Hirsch, K. A.; Zeyfang, D. *Chem. Ber.* **1970**, *103*, 222. (b) Jutz, C.; Rudolf, R. M.; Loebering, H. G. *Angew. Chem.* **1974**, *86*, 781.

(8) Pepin, Y.; Nazeme, H.; Payette, D. *Can. J. Chem.* **1978**, *56*, 41.

(9) (a) Nair, V.; Cooper, C. S. *J. Org. Chem.* **1981**, *46*, 4579. (b) Nair, V.; Jahnke, T. S. *Synthesis* **1984**, 424.

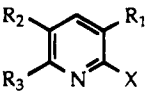
(10) The salt 1,1,5,5-tetramethyl-1,5-diazapentadienium chloride was prepared from β-(dimethylamino)acrolein (Fluka) and dimethylamine hydrochloride. Yields are generally not better than 50%.[8]

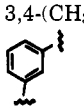
(11) Ege, G.; Frey, H. O.; Schuck, E. *Synthesis* **1979**, *5*, 376.

(12) Lesher, G. Y.; Opalka, C. J. U.S. Patent 4 137 233, 1979. *Ibid.* U.S. Patent 4 107 315, 1978; *Chem. Abstr.* **1979**, *90*, 103844.

(13) Arnold, Z. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3051. For a review of the Vilsmeier-Haack reaction, see: *Imminium Salts in Organic Chemistry*; Bohne, H., Jutz, C., Viehe, H. G., Eds.; Wiley-Interscience: 1976; Part 1, p 225. Coppola, G.; Hardtmann, G. E.; Huegi, B. S. *J. Heterocycl. Chem.* **1974**, *11*, 51.

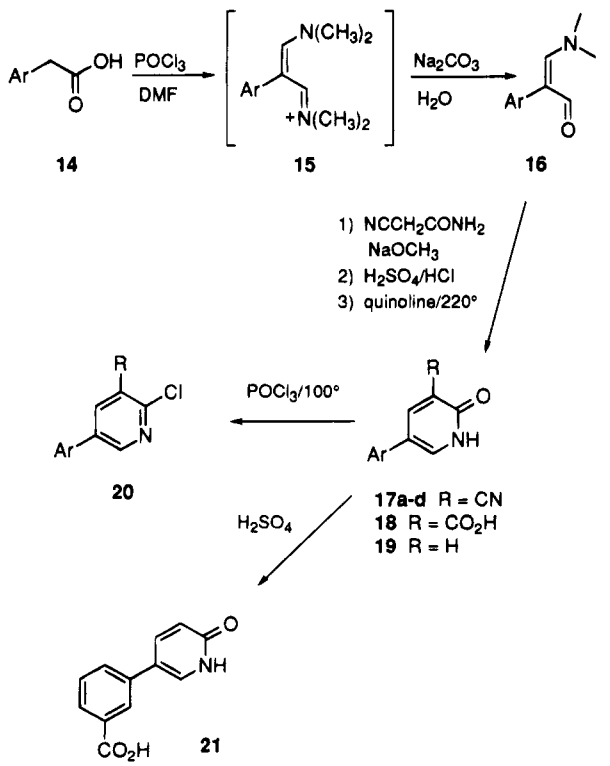
Table 2. Arylpyridines[a]



compd	R_1	R_2	R_3	X	mp, °C	procedure	recrystallization solvent	% yield
12a	3-pyridinyl	H	H	Cl	92–93.5	C	hexane	83
12b	3-CF_3-Ph	H	H	Cl	86–88	C	hexane	95
12c	3-CH_3O-Ph	H	H	Cl	oil	C		32
12d	phenyl	H	H	Cl	58–60	C	hexane	30
13a	3-(3-pyridinyl)	H	H	NH_2	116–118	N	hexane	93
13b	3-(3-CF_3-Ph)	H	H	NH_2	114–116	N	hexane	29
20a	H	3-pyridinyl	H	Cl	128–130	K	hexane	67
20b	H	3-CF_3-Ph	H	Cl	43–45[b]	K,H	CH_2Cl_2–hexane	69, 89
20c	H	2,4-Cl_2-Ph	H	Cl	152–155	K	CH_2Cl_2–hexane	72
20d	H	3,4-$(CH_3O)_2$-Ph	H	Cl	95–97	K	CH_2Cl_2–hexane	69
20e	H		H	Cl	204–206	K	CH_2Cl_2–CH_3OH	60
20f	H	4-NO_2-Ph	H	Cl	179–181	K	CH_2Cl_2–hexane	57
20g	H	2-CH_3-Ph	H	Cl	oil	K		89
20h	H	3-CH_3-Ph	H	Cl	62–63	K	hexane	70
20i	H	2,6-Cl_2-Ph	H	Cl	oil	K		90
20j	H	3-NO_2-Ph	H	Cl	183–184	K	CH_2Cl_2–hexane	55
20k	H	4-Cl	H	Cl	113–115	H	hexane	57
20l	H	4-F-Ph	H	Cl	115–116.5	H	CH_2Cl_2–hexane	62
20m	CO_2CH_3	3-CF_3-Ph	H	Cl	67–70	K	hexane	100
20n	SO_2Ph	3-CF_3-Ph	H	Cl	163–166	K	CH_2Cl_2–hexane	90
20o	CN	3-CF_3-Ph	H	Cl	109–111	K	CH_2Cl_2–hexane	99
20p	COPh	3-CF_3-Ph	H	Cl	148–150	K	CH_2Cl_2–hexane	42
20q	$COCH_3$	3-CF_3-Ph	H	Cl	76–78	K	CH_2Cl_2–hexane	40
20r	H	4-Ph	H	Cl	65[c]	H	hexane	51
23	5-(3-CF_3-Ph)	H	H	NH_2	99–101	N	hexane	75
30a	H	H	3-pyridinyl	Cl	58–60	M	hexane	77
30b	H	H	3-CF_3-Ph	Cl	oil	M		58
30c	H	H	3,4-$(CH_3O)_2$-Ph	Cl	89–91	M	CH_2Cl_2–hexane	11
30d	H	H	phenyl	Cl	oil	M		51

[a] Satisfactory analytical data (±0.4% for C,H,N, etc.) were obtained for all new compounds. [b] Lit.[2] mp 40–42 °C. [c] Lit.[21] mp 65–66 °C.

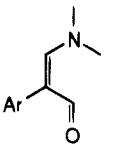
Scheme 2



Hydrolysis of **17** with refluxing 80% sulfuric acid was satisfactory except in the case of the 3-(trifluoromethyl)-phenyl derivative **17b**, in which both the trifluoromethyl group and the nitrile group were hydrolyzed to carboxylic acids to give pyridone **21** (*in situ* decarboxylation; Table 4). A 1:1 mixture of concentrated hydrochloric acid and glacial acetic acid was found to be the method of choice for hydrolysis of the nitrile group in this case and to be universally the best method. Decarboxylation by heating the carboxylic acids **18** in refluxing quinoline cleanly produced the desired 5-aryl-2-pyridones **19** (Table 4). Copper catalysis (CuO) appeared to be of no advantage in these decarboxylations. Heating alone without solvent (internal temperature 290–300 °C) for 2.5 h also smoothly effected decarboxylation. Reaction of **19** with phorphorus oxychloride afforded the 5-aryl-2-chloropyridines **20** (Table 2).

Although this sequence of reactions (Scheme 2) was adequate for the preparation of 5-substituted and un-

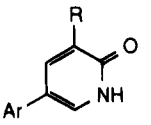
Table 3. 2-Aryl-3-(dimethylamino)-2-propenals 16[a]



compd	Ar	mp °C	recrystallization solvent	% yield[b]
16a	4-Cl-Ph	121–124	CH_2Cl_2–hexane	57
16b	3-F-Ph	42–43.5	ether	70
16c	3-CF_3-Ph	128–131.5	CH_2Cl_2–hexane	70
16d	4-F-Ph	87.5–91.5	CH_2Cl_2–hexane/ether	69

[a] Prepared according to general procedure D; see experimental. [b] Satisfactory analytical data (±0.4% for C,H,N, etc.) were obtained for all new compounds.

Table 4. 5-Aryl-2-oxopyridines 17–19



compd	Ar	R	mp, °C	procedure	recrystallization solvent	% yield[a]
17a	4-Cl-Ph	CN	>300	E	acetic acid–water	75
17b	3-F-Ph	CN	261–266	E		75[b]
17c	3-CF_3-Ph	CN	242–246	E		80[c]
17d	4-F-Ph	CN	300–303	E		44[d]
17e	Ph	CO_2CH_3	221–224	E		46[d]
17f	3-CF_3-Ph	CO_2CH_3	195–201	E		43[d]
17g	3-CF_3-Ph	$CO_2CH_2CH_3$	159–160	E		14[d]
17h	3-CF_3-Ph	$CONH_2$	276.5–278.5	E		28[e]
18a	4-Cl-Ph	CO_2H	320–322	F		84[d]
18b	3-F-Ph	CO_2H	315–318	F		79[d]
18c	Ph	CO_2H	296 dec	F		79[f]
18d	3-CF_3-Ph	CO_2H	296–299	F		96[f]
18e	4-F-Ph	CO_2H	>310	F		92[f]
19a	4-Cl-Ph	H	180–182.5	G	$CHCl_3$–hexane	68
19b	3-F-Ph	H	171–173	G	$CHCl_3$–hexane	44
19c	Ph	H	173–177	G	$CHCl_3$–hexane	89
19d	3-CF_3-Ph	H	172–174	G	$CHCl_3$–hexane	71
19e	4-F-Ph	H	168.5–171.5	G	$CHCl_3$–hexane	66

[a] Satisfactory analytical data (±0.4% for C,H,N, etc.) were obtained for all new compounds. The analysis of compound **17a** was consistant with the presence of 0.75 mol of water, and the analysis of compound **18a** was consistant with the presence of 0.25 mol of water. [b] Solid from reaction mixture washed with water, ethanol, and ether. [c] Solid from reaction mixture washed with ethanol, ether, and hexane. [d] Solid precipitated in reaction mixture, suspended in water, and 10% HCl added to give a white solid which was washed with water. [e] Solid from reaction mixture washed with CH_3OH. [f] Solid from reaction mixture washed with water and ethanol.

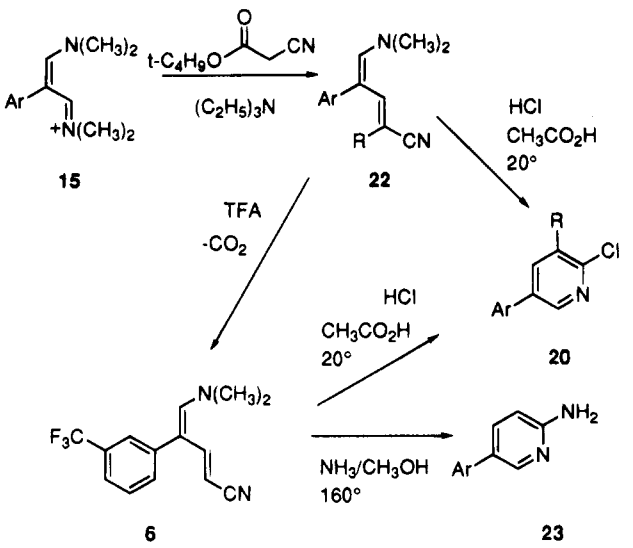
substituted phenyl-2-chloropyridines, it was in general lengthy and unsuitable for the preparation of **20a** where Ar = 3-pyridyl. In this case it was found that the intermediate propenal **16** could be prepared, but it was difficult to purify and reacted poorly with cyanoacetamide.[12] The solution to both problems was to use the more reactive diformylation/decarboxylation intermediate **15** for reaction with a cyanoacetamide equivalent. Since we suspected from the preparation of the 3-aryl-2-chloropyridines **12** that two electron-withdrawing groups at the terminus of the diene were not necessary for efficient cyclization with hydrochloric acid, a replacement for cyanoacetamide was chosen that would allow for the removal of the second electron-withdrawing group before cyclization. This would avoid the hydrolysis and decarboxylation steps seen in Scheme 2.

Extended heating (72 h at 80 °C) of 3-pyridineacetic acid hydrochloride, **14a**, with 2.2 equiv of Vilsmeier reagent (dimethylformamide and oxalyl chloride) in dimethylformamide followed by *in situ* condensation with *tert*-butyl cyanoacetate and triethylamine affords the dienylnitrile **22a** (R = CO_2-*t*-Bu) (Scheme 3). In those cases where aryl is not 3-pyridyl, the Vilsmeier diformylation/decarboxylation (phorphorus oxychloride and dimethylformamide) is usually complete after heating for 2–3 h at 80 °C (Table 5). The iminium salts **15** can be isolated as the solid perchlorate salts (except when Ar = 3-pyridyl[14]) by addition of the reaction medium to aqueous sodium perchlorate. These salts could then be treated with *tert*-butyl cyanoacetate and either potassium carbonate in ethanol or triethylamine in dimethylformamide to give the dienyl nitriles **22** (Table 6). While the stereochemistry about the double bonds in **22** is not known, only one isomer was obtained in each case.

Treatment of dienylnitriles **22** with hydrochloric acid in glacial acetic at 20 °C effected deblocking of the ester, decarboxylation, and cyclization to give the chloro-

(14) When Ar = 3-pyridinyl, the perchlorate salt is water soluble.

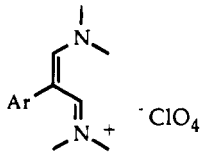
Scheme 3



pyridines **20** (R = H) in good to excellent yields (Table 2). The yield of **20** (R = H) is much lower if the reaction is conducted at 60 °C. In contrast to the preparation of the 3-aryl-2-chloropyridines **12**, there was no significant difference in yields when the aryl group was electron donating, electron withdrawing, or 2,6-disubstituted.

The intermediacy of the decarboxylated diene **6** in the cyclization was clearly demonstrated in the following experiments. When the dienylnitrile **22b** (Ar = 3-CF_3-phenyl) was treated with hydrochloric acid in acetic acid and the reaction was quenched after 10 min, a mixture of **22b**, **6**, and **20b** (Ar = 3-CF_3-phenyl) was isolated. The dienylnitrile **6** could be isolated cleanly by treatment of **22b** with trifluoroacetic acid at 20 °C. Cyclization of **6** with hydrochloric acid in acetic acid proceeded as expected to give **20b**. In addition, **6** can be directly converted into 5-[3-(trifluoromethyl)phenyl]-2-amino-

Table 5. 1,5-Diazapentadienium Salts 15[a]



compd	Ar	mp, °C	recrystallization solvent	% yield[b]
15b	3-CF_3-Ph	141.5–143	CH_3OH–water	81
15c	2,4-Cl_2-Ph	188–190	CH_3OH–water	100
15d	3,4-(CH_3O)-Ph	147–148	water	87
15e		215–217	CH_3OH–water	81
15f	4-NO_2-Ph	226–228	CH_3OH–water	100
15g	2-CH_3-Ph	199–200	CH_3OH–water	52
15h	3-CH_3-Ph	164–166	water	94
15i	2,6-Cl_2-Ph	282–284	CH_3OH–water	96
15j	3-NO_2-Ph	176–178	CH_3OH	84

[a] Prepared according to general procedure I; see experimental. [b] Satisfactory analytical data (±0.4% for C,H,N or high-resolution mass spetcra) were obtained for all new compounds.

pyridine, **23**, by treatment with ammonia in methanol as described above (Table 2).

3-Substituted-5-aryl-2-chloropyridines **20m–q** (R ≠ H) can be prepared by reaction of iminium salts **15** with substituted acetonitriles followed by ring closure with hydrochloric acid–acetic acid (Scheme 3, Table 2). For example, **15b** reacted with methyl cyanoacetate (dimethylformamide–triethylamine) to give **22k** (99%, Table 6) which was cyclized at 20 °C to 2-chloropyridine **20m** in nearly quantitative yield (Table 2). In a similar manner, (phenylsulfonyl)acetonitrile and malononitrile were condensed with **15b** and the products then cyclized to the 2-chloropyridines **20n,o**, respectively, in good yield. Ketones behaved somewhat differently. Benzoylacetonitrile condensed with **15b** in dimethylformamide with triethylamine in only modest yield. The sodium anion of acetylacetonitrile[15] condensed with **15b** in somewhat better yield. Both ketone dienylnitriles cyclized in a sluggish fashion to afford modest yields of the 2-chloropyridines **20p,q**, respectively.

6-Aryl-2-chloropyridines. Acetophenones **24** can be converted in one pot into dienylnitriles **28** via a modification of the method of Liebscher and Hartmann[16] (Scheme 4). Liebscher reported that acetophenones were converted with 2 equiv of Vilsmeier reagent into the aryl-substituted β-chlorovinylmethimonium salts **26** which could be isolated as the perchlorate salts.[16] Alternatively, enaminones **25**, which could be prepared from **24** with dimethylformamide dimethylacetal,[17–20] were converted with 1 equiv of Vilsmeier reagent into **26**. The most streamlined procedure employs the use of 2 equiv of Vilsmeier reagent generated from oxalyl chloride in dimethylformamide followed by the *in situ* condensation of the intermediate **26** with *tert*-butyl cyanoacetate and excess triethylamine (Table 6). Under these conditions, **27** reacts with the dimethylamine released during the condensation to form the dienyl nitriles **28**.

Cyclization of **28** with hydrochloric acid in acetic acid is a slow process, requiring stirring at 20 °C for 4 days for complete conversion to chloropyridines **30** (Table 2). If the reaction is quenched after 15 min, an inseparable 1:1 mixture of two decarboxylated isomers can be isolated, **29a,b** (81%). NMR reveals these two isomers to be a mixture of cis and trans isomers about the alkene adjacent to the nitrile. This slow rate of cyclization is in contrast to the reaction of **22**, where the cyclization of **6** proceeds at nearly the same rate as the decarboxylation of **22**. In contrast to the cyclization of **22**, in which there is no significant difference in yield between electron poor and electron rich aromatic substituents, there is a significantly lower yield for the cyclization of electron rich aromatic aryl diene **28c** (aryl = 3,4-(CH_3O)$_2$-phenyl).

For comparison, a phenyl-substituted chloro analog from Ponticello *et al.* was prepared. Treatment of the dienyldinitrile **31**[6] with hydrochloric acid in acetic acid at 20 °C for 12 h affords the 2-chloro-3-cyano-4-phenylpyridine, **32a,** in 98% yield (Figure 4). By comparison, Ponticello reports that treatment of **31** with HBr in acetic acid at 60 °C results in a 22% yield of **32b.**[6] At this time it is not clear whether the difference in yield is due to a variation in the temperature or the reagent.

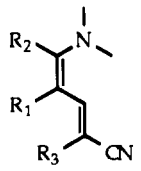
Discussion

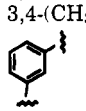
There are some interesting differences in the rates and yields of cyclization of the three dienylnitriles **5–7**. The difference in yields between electron-donating (**5c,d**) and electron-withdrawing (**5a,b**) phenyl groups in the cyclization of **5** can be explained in terms of the addition–elimination mechanism proposed by Bryson *et al.* One might expect, that with an aryl group substituting for the ester in **8**, that electron-donating aryl groups would retard delocalization into the diene thereby allowing the intermediate haloimine opportunity to find other paths for decomposition. Electron-withdrawing aryl groups would act much like the ester. This would explain the 2-fold difference in yields. However, one would expect that **6**, with the aryl groups directly conjugated to the amine, would also display this trend. Either the latter cyclization proceeds through a different mechanism or the phenyl group is not in conjugation with the diene during cyclization and thereby contributes little. In fact the similarity in yield between the 2,6-dichlorophenyl derivative **22i**, where the α,α′ disubstitution precludes a planar arrangement of the diene and the phenyl ring, and those derivatives with no substitution in the 2,6 position would indicate that conjugation of the aryl group with the diene is of little importance in the cyclization of **6**. Since the aryl group in **7** is not in conjugation with the amine, we would expect and in fact see little difference in the yield of cyclization with different aryl groups. The sluggishness of the cyclization of **7** is more than likely due to the hindrance of approach of the chloroimine to the diene terminus by the aryl group.

In conclusion, we have presented several routes for the preparation of 3-, 5-, or 6-aryl-2-chloropyridines in two to six steps, in moderate to high yields, from readily available starting materials. The most efficient route to the preparation of the 5-aryl-2-chloropyridines relies upon the use of the unsubstituted aryl nitrile **6**, which is conveniently prepared *in situ* by deblocking and decarboxylation of the precursor *tert*-butyl ester during

(15) Hanifin, J. W.; Ridge, D. N. U.S. Patent 4 173 650, 1979; *Chem. Abstr.* **1980**, *92*, 76142.
(16) Liebscher, J.; Hartmann, H. *J. Prakt. Chem.* **1976**, *318*, 731.
(17) Bredereck, H.; Effenberger, F.; Botsch, H. *Chem. Ber.* **1964**, *97*, 3397.
(18) Junek, H.; Schmidt, A. *Monatsh. Chem.* **1968**, *99*, 635.
(19) Junek, H.; Stoly, G. *Monatsh. Chem.* **1970**, *101*, 1234.
(20) Lin, Yang-i; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1977**, *14*, 345.
(21) Adams, W. J.; Hey, D. H.; Mamalis, P.; Parker, R. E. *J. Chem. Soc.* **1949**, 318.

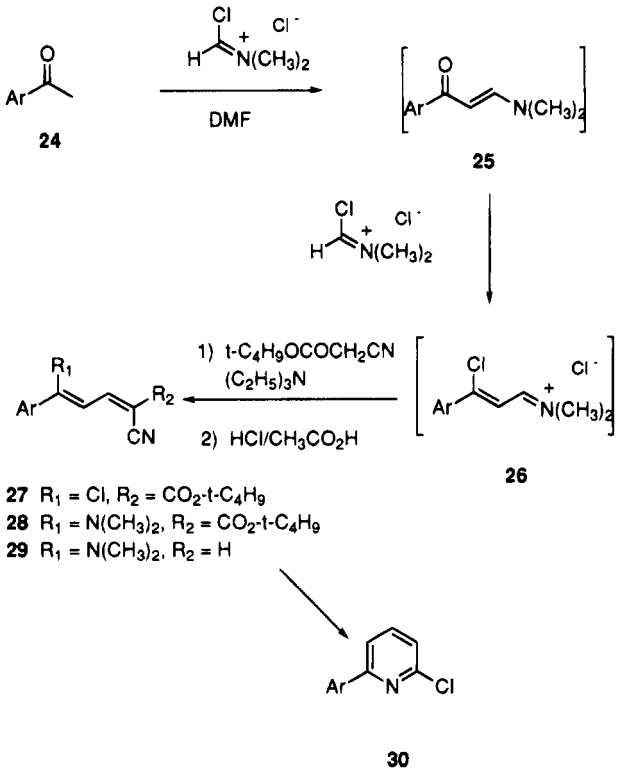
Table 6. 2-Cyano-5-(dimethylamino)aryl-2,4-pentadienes[a]



compd	R_1	R_2	R_3	mp, °C	procedure	recrystallization solvent	% yield
22a	3-pyridinyl	H	CO_2-*t*-C_4H_9	161–163	J	ether–hexane	72[b]
22b	3-CF_3-Ph	H	CO_2-*t*-C_4H_9	129–131	J	ethyl acetate–hexane	94
22c	2,4-Cl_2-Ph	H	CO_2-*t*-C_4H_9	145–147	J	CH_2Cl_2–hexane	72
22d	3,4-$(CH_3O)_2$-Ph	H	CO_2-*t*-C_4H_9	163–166	J	CH_2Cl_2–hexane	89
22e		H	CO_2-*t*-C_4H_9	204–206	J	CH_2Cl_2–hexane	65
22f	4-NO_2-Ph	H	CO_2-*t*-C_4H_9	210–213	J	CH_2Cl_2–hexane	85
22g	2-CH_3-Ph	H	CO_2-*t*-C_4H_9	157–159	J	ethyl acetate–hexane	90
22h	3-CH_3-Ph	H	CO_2-*t*-C_4H_9	129–131	J	ethyl acetate–hexane	76
22i	2,6-Cl_2-Ph	H	CO_2-*t*-C_4H_9	198–200	J	ethyl acetate–hexane	75
22j	3-NO_2-Ph	H	CO_2-*t*-C_4H_9	162–165	J	ethyl acetate–hexane	84
22k	3-CF_3-Ph	H	CO_2CH_3	211–212	J	CH_2Cl_2–hexane	99
22l	3-CF_3-Ph	H	SO_2Ph	170–172	J	CH_2Cl_2–hexane	91
22m	3-CF_3-Ph	H	CN	149–153	J	CH_2Cl_2–hexane	77
22n	3-CF_3-Ph	H	COPh	148–151	J	CH_2Cl_2–hexane	41
22o	3-CF_3-Ph	H	$COCH_3$	196–197	J	CH_2Cl_2–hexane	79
28a	H	3-pyridinyl	CO_2-*t*-C_4H_9	136–140	L	CH_2Cl_2–hexane	30
28b	H	3-CF_3-Ph	CO_2-*t*-C_4H_9	152–154	L	CH_2Cl_2–hexane	55
28c	H	3,4-$(CH_3O)_2$-Ph	CO_2-*t*-C_4H_9	169–170	L	CH_2Cl_2–hexane	28
28d	H	phenyl	CO_2-*t*-C_4H_9	142–145	L	CH_2Cl_2–hexane	73

[a] Satisfactory analytical data (±0.4% for C,H,N, etc.) were obtained for all new compounds. [b] Prepared from 3-pyridylacetic acid hydrochloride; see experimental.

Scheme 4



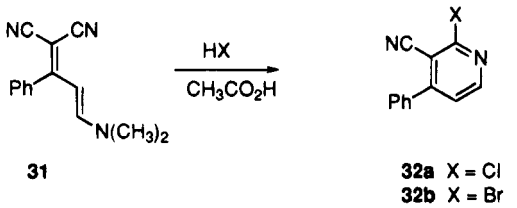


Figure 4.

the cyclization. It appears that two electron-withdrawing groups are not necessary for efficient cyclization to chloropyridines. In addition, the intermediates **5** or **6** can be converted directly into 2-aminopyridines.

Experimental Section

General. Melting points are uncorrected. DMF was stored over 4 Å molecular sieves. THF was distilled from benzophenone sodium. Diisopropylamine and triethylamine were distilled from calcium hydride. Acetonitrile was sequentially distilled from phosphorus pentoxide followed by potassium carbonate. Bredereck's reagent and β-(dimethylamino)acrolein were purchased from Fluka. Preparative layer chromatography (PLC) was performed on Analtech silica gel GF 2000 μm plates. Column chromatography silica gel was Davidson 60–200 mesh.

α-Ethylidene-3-pyridineacetonitrile (11a). General Procedure A. 3-Pyridineacetonitrile (57.0 g, 470 mmol), acetaldehyde (23.3 g, 529 mmol), and $CsCO_3$ (0.5 g, 1.5 mmol) were dissolved in absolute ethanol (1000 mL). The solution was stirred at 20 °C for 30 h and then partitioned between water (2 L) and ether (1 L). The aqueous phase was extracted with ether (3 × 1 L) and then ethyl acetate (500 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed at reduced pressure to yield an orange oil. Chromatography (silica gel, 500 g, ethyl acetate/hexane (1:1)) yielded a pale yellow oil (33.9 g, 50%) which was crystallized from CH_2Cl_2/hexane to give white needles: mp 46.5–47.5 °C; NMR ($CDCl_3$) δ 2.26 (d, J = 7.1 Hz, 3H), 7.0 (q, J = 7.1, 1H), 7.34 (dd, J = 8.0, 4.8 Hz, 1H), 7.81 (apparent dt, J = 8.0, 2.1 Hz, 1H), 8.59 (dd, J = 4.8, 1.4 Hz, 1H), 8.78 (d, J = 2.3 Hz, 1H).

***(E,Z)*-α-[3-(Dimethylamino)-2-propenylidene]-3-pyridineacetonitrile (5a). General Procedure B.** *tert*-Butoxybis(dimethylamino)methane (0.315 mL, 1.5 mmol) and **11a** (0.17 g, 1.3 mmol) were dissolved in THF (6 mL) and stirred at 20 °C for 20 h. The solvent was removed at reduced pressure and the orange oil purified via PLC (ethyl acetate/hexane (10:3)). A yellow solid was obtained (0.26 g, 94%)

which was recrystallized from CH_2Cl_2/hexane to give yellow crystals: mp 117–120 °C; NMR ($CDCl_3$) δ 3.0 (s, 6H), 5.57 (t, J = 12.1 Hz, 1H), 6.85 (d, J = 12.5 Hz, 1H), 7.35 (m, 2H), 7.7 (m, 1H, 8.37 (dd, J = 4.8, 1.5 Hz, 1H), 8.7 (d, J = 2.4 Hz, 1H).

(*E,Z*)-α-[3-(Dimethylamino)-2-propenylidene]-3-(trifluromethyl)benzeneacetonitrile (5b) (from 10b). Diisopropylamine (0.4 mL, 3 mmol) was dissolved in dry THF (100 mL) under argon and cooled to 0 °C. *n*-Butyllithium (2.7 M, 1.05 mL, 2.8 mmol) was added via syringe and the solution stirred at 0 °C for 15 min. 3-(Trifluoromethyl)phenylacetonitrile (0.5 g, 2.7 mmol) in THF (5 mL) was added dropwise via cannula over 5 min. The brown solution was stirred at 0 °C for 10 min. Dry triethylamine (33.8 mL, 27 mmol) and 1,1,5,5,-tetramethyl-1,5-diazapentadienium chloride (0.78 g, 2.7 mmol) were combined and added in one portion. The solution was allowed to warm to rt and stirred for 6 h. The reaction mixture was poured into brine and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed at reduced pressure to afford an orange oil. Purification via PLC (CH_2Cl_2/hexane (3:2)) afforded orange crystals (0.36 g, 50%): mp 117–118 °C; NMR ($CDCl_3$) δ 3.0 (s, 6H), 5.5 (t, J = 12.1, 1H), 6.86 (d, J = 12.5 Hz, 1H), 7.26 (d, J = 11.7 Hz, 1H), 7.4 (m, 2H), 7.65 (m, 1H), 7.65 (s, 1H).

3-[3-(Trifluoromethyl)phenyl]-2-chloropyridine (12b). General Procedure C. A solution of **5b** (9.2 g, 43 mmol) in glacial acetic acid (100 mL) was heated to 60 °C. To this solution was added dry HCl gas at a moderate rate for 2 min. The solution was heated at 60 °C for 2 h and then poured onto ice (100 g) and CH_2Cl_2 (100 mL). Solid K_2CO_3 was added until the solution was basic and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed at reduced pressure to afford pink crystals (3 g). Purification via column chromatography (ethyl acetate/hexane (1:6)) afforded a crystalline mass. Recrystallization from hexane afforded colorless crystals (2.0 g, 65%): mp 86–88 °C; NMR ($CDCl_3$) δ 7.36 (dd, J = 7.6, 4.8 Hz, 1H), 7.7 (m, 5H), 7.45 (dd, J = 4.8, 1.9 Hz, 1H).

3-(Dimethylamino)-2-[3-(trifluoromethyl)phenyl]-2-propenal (16c). General Procedure D. To a solution of Vilsmeier reagent prepared from DMF (182.5 g, 2.5 mol) and $POCl_3$ (210 mL, 2.25 mol) at 10–15 °C was added 3-(trifluoromethyl)phenylacetic acid (101 g, 0.5 mol). The mixture was stirred and heated at 60–70 °C for 8 h. After cooling to rt, the mixture was added slowly to a mixture of ice and water with external cooling and ice added intermittently to keep the temperature < 10 °C. When the drowning was complete, K_2CO_3 and ice were added slowly until pH 11 was achieved. Small quantities of ethanol were added to control frothing. To the alkaline mixture was added 500 mL of toluene, and the mixture was refluxed for 1.5 h and cooled to rt. The aqueous layer was extracted with an additional 500 mL of toluene. The combined organic layers were washed with water and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure gave tan crystals which were recrystallized from CH_2Cl_2/hexane to give 83.7 g (70%) of yellow prisms: mp 128–133 °C; NMR ($CDCl_3$) δ 2.8 (bs, 6H), 6.87 (bs, 1H), 7.45 (m, 4H), 9.1 (s, 1H).

1,2-Dihydro-2-oxo-5-[3-(trifluoromethyl)phenyl]-3-pyridinecarbonitrile (17c). General Procedure E. To a solution of sodium methoxide (72.4 g, 1.34 mol) in 1300 mL of CH_3OH was added cyanoacetamide (54.7 g, 1.64 mol) followed by **16c** (138.5 g, 0.57 mol). The mixture was stirred at rt for 1.5 h and then refluxed overnight during which time a yellow solid separated. Water was added, and the mixture was acidified and filtered to remove a yellow solid which was washed with water, ethanol, ether, and then hexane to give 116.4 g (77%) of product: mp 238–244 °C; NMR ($CDCl_3$) δ 7.62 (m, 3H), 7.66 (m, 1H), 7.83 (d, J = 3.4 Hz, 1H), 8.18 (d, J = 3.4 Hz, 1H), 13.0 (bs, 1H).

1,2-Dihydro-2-oxo-5-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxylic Acid (18d). General Procedure F. A mixture of **17c** (38.7 g, 0.146 mol) in 600 mL of acetic acid and 400 mL of concd HCl was refluxed for 18 h and then diluted with 100 mL of water. After stirring and cooling, the mixture was filtered, and the solid was washed with water and ethanol to give 37.7 g (91%) of off-white crystals: mp 300–305 °C dec; NMR ($CDCl_3$) δ 7.65 (m, 2H), 7.75 (m, 2H), 7.95 (d, J = 2.4 Hz, 1H), 8.75 (dd, J = 0.5 Hz, 1H), 13.5 (bs, 1H), 14.6 (bs, 1H).

5-[3-(Trifluoromethyl)phenyl]-2(1*H*)-pyridone (19d). General Procedure G. A mixture of **18d** (42.5 g, 150 mmol) and 175 mL of quinoline was heated for 12 h at 220 °C under argon, cooled, and then poured into 2 L of hexane with external cooling. Filtration yielded a tan solid which was recrystallized from $CHCl_3$/hexane to afford 28.4 g (79%) of pale yellow needles: mp 174–178 °C; NMR ($CDCl_3$) δ 6.7 (d, J = 9.5 Hz, 1H), 7.6 (m, 5H), 7.8 (dd, J = 9.5, 3.7 Hz, 1H), 13.0 (bs, 1H).

3-(1,6-Dihydro-6-oxo-3-pyridyl)benzoic acid (21). A mixture of **17c** (56.5 g, 0.214 mol) and 975 mL of 80% sulfuric acid was refluxed for 8 h. After cooling to rt, the solution was poured onto 1.0 L of water and filtered to remove a white solid. The solid was dissolved in 500 mL of 1 N sodium hydroxide and filtered. The filtrate was brought to pH 1 with hydrochloric acid and filtered. The white solid obtained was dried under vacumn to afford 50.4 g (83%) of white microcrystals. A small sample was sublimed under high vacuum and at 380 °C to afford very pale yellow crystals: mp 370–375 °C dec; NMR ($CDCl_3$) δ 6.45 (d, J = 9.5 Hz, 1H), 7.5 (t, J = 7.7 Hz, 1H), 7.85 (m, 4H), 8.05 (t, J = 1.5 Hz, 1H), 12.6 (bs, 2H).

Preparation of 19d by Thermolysis. To a 1 L recovery flask, fitted with a gas outlet tube and rubber connection to a bubbler, was added **18b** (100 g, 0.35 mol). The flask was immersed in a Wood's metal bath at 320 °C and kept at 290–300 °C (internal temperature) for 2.5 h while monitoring the evolution of CO_2. The flask was cautiously swirled on occasion (gas evolution ceased after *ca.* 2 h). The hot brown melt was poured carefully (splattering) into 800 mL of vigorously stirred $CHCl_3$ and the warm solution filtered through 100 g of hydrous magnesium silicate (600 mL sintered glass funnel) which was washed with an additional 400 mL of $CHCl_3$. The filtrate was diluted to 3 L with hexane, cooled overnight, and filtered to give 60.4 g (83%) of crystals: mp 174–178 °C.

2-Chloro-5-[3-(trifluoromethyl)phenyl]pyridine (20b). General Procedure H. A mixture of 29.4 g (0.123 mol) of **19d** and 125 mL of $POCl_3$ was refluxed overnight. The excess $POCl_3$ was removed under vacuum, toluene was added, and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 and poured into a slurry of ice and water. After standing, the organic layer was separated, washed with H_2O and saturated $NaHCO_3$, and dried ($MgSO_4$). Removal of the solvent gave a red oil which was dissolved in CH_2Cl_2, and the solution was filtered through silica gel. Evaporation of the filtrate gave 28.3 g (89%) of white crystals: mp 40–42 °C; NMR ($CDCl_3$) δ 7.4 (d, J = Hz, 1H), 7.8 (m, 4H), 7.8 (dd, J = 8.3, 2.6 Hz, 1H), 8.6 (d, J = 2.3 Hz, 1H).

(*E*)-*N*-[3-(Dimethylamino)-2-[3-(trifluoromethyl)phenyl]-2-propenylidene]-*N*-methylmethanaminium monoperchlorate (15b). General Procedure I. $POCl_3$ (92 g, 0.6 mol) was added over 1 h to anhydrous DMF (220 g, 3 mol) while keeping the temperature at 15–20 °C. After the solution had stirred at rt for 1 h, 3-(trifluoromethyl)phenylacetic acid (40.8 g, 0.2 mol) was added. The solution was warmed to 85 °C and stirred for 18 h. The solution was cooled to rt and poured onto 600 g of ice with vigorous stirring. A solution of sodium perchlorate (36.6 g, 0.3 mol) in water (80 mL) was added, and a crystalline precipitate formed over 10 min. The precipitate was filtered, washed with water, and dried *in vacuo* at 50 °C to afford a tan powder (60.4 g). This material was sufficiently pure to use for further experiments; however an 8 g portion was recystallized from CH_3OH/water to afford an off white solid (5.8 g): mp 141.5–143 °C. While we observed no explosive behavior with any of our perchlorate salts, it is a potential hazard, and adequate precautions (small sample sizes, safety shields, and proper clothing) should be used when drying and using them. **15b**: NMR δ 4.6 (bs, 2H), 6.77 (dd, J = 7.4, 5 Hz, 1H), 7.36 (dd, J = 7.4, 1.8 Hz), 7.63 (m, 3H), 8.1 (dd, J = 5.0, 1.8 Hz, 1H).

(*E,Z*)-1,1-Dimethylethyl 2-Cyano-5-(dimethylamino)-4-[3-(trifluoromethyl)phenyl]-2,4-pentadienoate (22b). General Procedure J. To a solution of **15b** (unrecrystallized

material from general procedure I) (2 g, 5.4 mmol) dissolved in DMF (200 mL) were added *tert*-butyl cyanoacetate (0.84 g, 5.9 mmol) and triethylamine (0.87 mL, 5.9 mmol). The solution was stirred at rt for 18 h and then partitioned between water (300 mL) and CH_2Cl_2 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$). The volatiles were removed at reduced pressure, and the yellow-brown residue was purified via chromatography (hydrous magnesium silicate, ethyl acetate/hexane (1:3)). The yellow solid obtained was recrystallized from CH_2Cl_2/hexane to afford yellow crystals (1.78 g, 94%): mp 129–131 °C; NMR ($CDCl_3$) δ 1.47 (s, 9), 2.7 (bs, 6H), 7.05 (bs, 1H), 7.45 (m, 3), 7.63 (d, J = 7.7 Hz, 1H), 7.72 (s, 1H).

(*E,Z*)-1,1-Dimethylethyl 2-Cyano-5-(dimethylamino)-4-(3-pyridyl)-2,4-pentadienoate (22a). To a 0 °C solution of CH_2Cl_2 (300 mL) and DMF (13.4 mL, 172 mmol) was added oxalyl chloride (11.1 mL, 126 mmol) in CH_2Cl_2 (50 mL) dropwise. White flocculent solids precipitated out of solution, and there was copious gas evolution. After the addition was complete, the solution was allowed to warm to 25 °C over 30 min. The volatiles were removed at reduced pressure to afford white solids. To the solids were added 3-pyridineacetic acid hydrochloride (10 g, 58 mmol) and DMF (30 mL). The solution was stirred at 25 °C for 30 min and then warmed to 80 °C for 3 days. The black solution was cooled to 0 °C and *tert*-butyl cyanoacetate (8.13 g, 58 mmol) in DMF (50 mL) was added followed by the dropwise addition of triethylamine (35 mL, 259 mmol) over 5 min. The solution was stirred at 0 °C for 15 min and then allowed to warm to 25 °C and stirred for 1 h. The solution was poured into water (200 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The volatiles were removed at reduced pressure, and the residue was passed through a short column of hydrous magnesium silicate using first ethyl acetate and then acetone/hexane (1:1). The fractions containing product were further purified via preparative HPLC using acetone/hexane (2:3) to afford a yellow oil (12.4 g, 72%) that was pure by TLC and NMR. A portion was recrystallized from ether/hexane to afford canary yellow crystals: mp 161–163 °C; NMR δ 1.5 (s, 9), 2.85 (bs, 6H), 7.1 (s, 1H), 7.3 (m, 1H), 7.55 (d, t, J = 7.8, 2 Hz, 1H), 7.74 (s, 1H), 8.47 (d, J = 1.8 Hz, 1H), 8.61 (dd, J = 4.8, 1.6 Hz, 1H).

2-Chloro-5-[3-(trifluoromethyl)phenyl]pyridine (20b). General Procedure K. To a solution of **22b** (2.7 g, 7.6 mmol) in acetic acid (15 mL) was added gaseous HCl at a moderate rate for 15 min at rt. The solution was stirred at rt for 18 h and then partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined layers were dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue passed through a short pad of hydrous magnesium silicate (CH_2Cl_2/hexane (1:9)). The solvent was removed at reduced pressure to afford a white crystalline mass (1.3 g, 69%). This material was identical to the material prepared from **19d**.

(*E,Z*)-5-(Dimethylamino)-4-[3-(trifluoromethyl)phenyl]-2,4-pentadienenitrile (6). The dienylnitrile **22b** (10.5 g, 28 mmol) was dissolved in trifluoroacetic acid (150 mL) and stirred at rt for 1 h. The volatiles were removed under reduced pressure at rt, and the black residue was partitioned between CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue purified via column chromatography (CH_2Cl_2/hexane (9:1) and then CH_2Cl_2/hexane (4:1)). The orange solid obtained (4.4 g) was recrystallized from CH_2Cl_2/hexane to afford orange-yellow needles (4.0 g, 53%): mp 83–86 °C; NMR ($CDCl_3$) δ 2.6 (s, 6H), 4.1 (d, J = 15 Hz, 1H), 6.5 (s, 1H), 7.0 (d, J = 15 Hz, 1H), 7.5 (m, 4H). Treatment of **6** (0.57 g, 2.15 mmol) under general procedure K afforded **20b** (0.46 g, 84%) identical to that prepared from **22b**.

(*E,Z*)-2-Cyano-5-(dimethylamino)-5-[3-(trifluoromethyl)phenyl]-2,4-pentadienoic Acid 1,1-Dimethylethyl Ester (28b). General Procedure L. To a solution of DMF (100 mL) was added oxalyl chloride (5.1 mL) in acetonitrile (5 mL) over 5 min. The viscous solution was stirred at rt for 10 min. To this solution was added 3-(trifluoromethyl)acetophenone (5 g, 26 mmol) in DMF (5 mL) over 2 min. The solution was stirred at rt for 20 h. To the clear yellow solution was added *tert*-butyl cyanoacetate (3.75 g, 32 mmol) in one portion followed by triethylamine (15.6 mL, 110 mmol) over 2 min. The solution was stirred at rt for 2 days and then partitioned between aqueous saturated $NaHCO_3$ (200 mL) and ether (200 mL). The aqueous layer was extracted with ether (3 × 100 mL), and the combined organic layers were washed with water (3 × 100 mL) and then brine. The organic layer was dried ($MgSO_4$), and the solvent was removed at reduced pressure. The yellow-orange residue was passed through a short column of hydrous magnesium silicate with CH_2Cl_2. The purified material (7.2 g) was recrystallized from CH_2Cl_2/hexane, affording fine yellow needles (5.36 g, 55%): mp 152–154 °C; NMR ($CDCl_3$) δ 1.42 (s, 9), 2.9 (bs, 3H), 3.2 (bs, 3H), 5.83 (d, J = 12.8 Hz, 1H), 7.19 (d, J = 12.9 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.48 (s, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H).

(*Z,E*)-5-(Dimethylamino)-5-[3-(trifluoromethyl)phenyl]-2,4-pentadienenitrile (29a) and (*E,E*)-5-(Dimethylamino)-5-[3-(trifluoromethyl)phenyl]-2,4-pentadienenitrile (29b). To a solution of acetic acid (50 mL) and **28b** was added HCl gas at a rapid rate for 1 min. The solution was stirred at 25 °C for 15 min and then poured onto a mixture of ice/water/CH_2Cl_2. The mixture was brought to a pH of >8 with solid K_2CO_3, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the volatiles were removed at reduced pressure. The residue was passed through a short column of hydrous magnesium silicate using CH_2Cl_2 to afford a brown oil (0.5 g, 81%). TLC in a variety of solvent systems showed a single compound. NMR ($CDCl_3$) showed a 1:1 mixture of **29a,b**. Cis isomer **29a**: δ 2.75 (s, 6H), 3.95 (d, J = 10.5 Hz, 1H), 5.3 (d, J = 11.8 Hz, 1H), 5.8 (dd, J = 10.5, 11.8 Hz, 1H), 7.0 (m, 2, 1H), 7.2 (m, 2H). Trans isomer **29b**: δ 2.75 (s, 6H), 4.4 (d, J = 15.3 Hz, 1H), 5.0 (d, J = 11.6 Hz, 1H), 6.0 (dd, J = 11.6, 15.3 Hz, 1H), 7.0 (m, 2H), 7.2 (m, 2H).

2-Chloro-6-(3-pyridyl)pyridine (30a). General Procedure M. To a solution of **28a** (2.6 g, 8.7 mmol) in acetic acid (200 mL) was added gaseous HCl at a rapid rate for 2 min at rt. The solution was stirred at rt for 4 days and then poured onto ice. The aqueous layer was brought to pH 12 with K_2CO_3 and extracted with CH_2Cl_2 (4 × 100 mL), and the combined layers were dried ($MgSO_4$). The solvent was removed at reduced pressure and the residual brown oil purified via column chromatography (CH_2Cl_2/CH_3OH (98:2)). This afforded a white solid (1.27 g, 77%) that was recrystallized from hexane to afford white needles: mp 58–60 °C; NMR δ 7.33 (d, J = 7 Hz, 1H), 7.39–7.44 (mm, 1H), 7.68–7.8 (m, 2H), 8.35 (d, t, J = 7, 2.1 Hz, 2H), 8.67 (dd, J = 4.7, 1.6 Hz, 1H), 9.18 (d, J = 2.1 Hz, 1H).

2-Chloro-4-phenyl-3-pyridinecarbonitrile (32a). 2-Cyano-5-(*N,N*-dimethylamino)-3-phenyl-2,4-pentadienenitrile[6] (1.1 g, 4.9 mmol) was dissolved in 100 mL of acetic acid. To this solution was added HCl gas at a rapid rate for 2 min. The solution was stirred at rt overnight and then poured onto ice (100 g). Solids which precipitated out of the solution were collected by filtration and washed with water. The solids were dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The first filtrate was basified with solid K_2CO_3 and then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed at reduced pressure. The off-white solid obtained (1.13 g) was dissolved in CH_2Cl_2 and passed through a short column of hydrous magnesium silicate with CH_2Cl_2. The volatiles were removed, and the white solids obtained (1.03 g, 98%) were pure by TLC and NMR and could be recrystallized from CH_2Cl_2/hexane to afford white crystals (0.87 g): mp 127.5–130 °C; NMR δ 7.66 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 8.1 (d, J = 8.1 Hz, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.3 (s, 1H).

3-(3-Pyridyl)-2-aminopyridine (13a). General Procedure N. A solution of **5a** (0.5 g, 2.5 mmol) was dissolved in 50 mL of anhydrous CH_3OH, and the solution was saturated with NH_3 with cooling to 0 °C. The solution was sealed in a

small steel bomb and heated to 150 °C for 100 h. The solution was cooled to rt, and the solvent was removed at reduced pressure. The residue was dissolved in CH_2Cl_2 and filtered to remove brown insoluble material. The solvent was removed at reduced pressure and the residue purified via PLC (CH_2Cl_2/CH_3OH (95:5), two elutions). The pale yellow oil/crystals obtained were recrystallized from CH_2Cl_2/hexane to afford fine pale yellow crystals (0.4 g, 93%): mp 116–118 °C; NMR δ 4.6 (bs, 2H), 6.78 (dd, J = 7.4, 5 Hz, 1H), 7.4 (m, 2H), 7.8 (d,t, J = 7.9, 2 Hz, 1H), 8.1 (dd, J = 5, 1.7 Hz, 1H), 8.62 (dd, J = 4.8, 1.5 Hz, 1H), 8.7 (d, J = 2.1 Hz, 1H).

Acknowledgment. We wish to thank L. Gehrlein and staff for elemental analysis and D. Cole and staff for spectral studies.

Supplementary Material Available: Elemental analysis for all new compounds (4 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9419706