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Iminopropadienones from Dioxanediones, Isoxazolopyrimidinones, Pyridopyrimidinones, and Pyridopyrimidinium Olates

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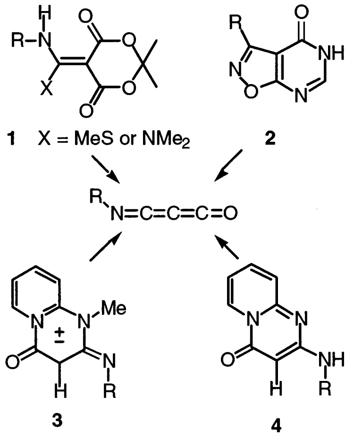
Iminopropadienones, RN=C=C=C=O, can be generated from four different types of precursors in flash vacuum thermolysis reactions: 1,3-dioxane-4,6-diones **1**, isoxazolopyrimidinones **2**, pyridopyrimidinium olates **3**, and pyridopyrimidinones **4**. 2,6-Difluorophenyl-, 2,6-diethylphenyl-, *o-tert*-butylphenyl-, and mesityliminopropadienone have been directly observed by Ar matrix IR spectroscopy in one or more of these reactions. Reactions with bis-nucleophiles afford pyridopyrimidinones and perhydrodiazepinone derivatives.

Introduction

We have reported the formation of iminopropadienones, RN=C=C=C=O, by flash vacuum thermolysis (FVT) of 1,3-dioxane-4,6-dione (Meldrum's acid) derivatives[1,2] **1** and, in a preliminary communication, isoxazolopyrimidinones **2**.[1] Pyridopyrimidinium olates of type **3** are obtained by addition of iminopropadienones to 2-(methylamino)pyridine, and in the case of the mesityl derivative, it was shown that compound **3** was again cleaved to mesityliminopropadienone and 2-(methylamino)pyridine on FVT.[2] We have now found that both mesoionic pyridopyrimidinium olates **3** and pyrimidopyrimidinones of type **4** can be used as precursors of a variety of aryliminopropadienones.



In this paper we report direct IR spectroscopic evidence for the formation of iminopropadienones from the four types of precursor, as well as the chemistry of two new derivatives, the 2,6-difluoro- and 2,6-diethylphenyliminopropadienones. Previous work has shown that mild steric hindrance can protect the iminopropadienones remarkably, thus making the neopentyl, the mesityl, and the *o-tert*-butylphenyl derivatives isolable at room temperature.[2] It was expected that electronegative substituents might increase the reactivity, and this has been borne out with the 2,6-difluorophenyl derivative. The 2,6-diethyl derivative, in contrast, was expected to show "normal" reactivity, like the mesityl derivative.[2]

Results and Discussion

2,6-Difluorophenyliminopropadienone **8** was generated from three different types of precursor, the Meldrum's acid derivatives **5** and **5′**, the isoxazolopyrimidinone **6**, and the mixture of isomeric pyridopyrimidinium olates **7a** and **7b** (Scheme 1). The Meldrum's acid precursor **5** was synthesized by reaction of 5-(bismethylthiomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione with 2,6-difluoroaniline, and **5′** was formed by further substitution of the SMe group by dimethylamine. Compound **6** was obtained from 2,6-difluorobenzaldehyde by adaptation of a standard procedure.[3] A 1:1 mixture of olates **7a** and **7b** was obtained by reaction of **8** (generated by preparative FVT of either **5** or **6**) with 2-(methylamino)pyridine (Scheme 1). Iminopropadienone **8** is not isolable, so the preparative chemistry of this compound is carried out by condensing the FVT product on a coldfinger at 77 K. After the end of the thermolysis, a solution of a trapping agent is injected onto the coldfinger, and the product is isolated after warming to room temperature. The two regioisomers **7a** and **7b** were not separable by chromatography, but the "normal" isomer **7a** crystallized selectively

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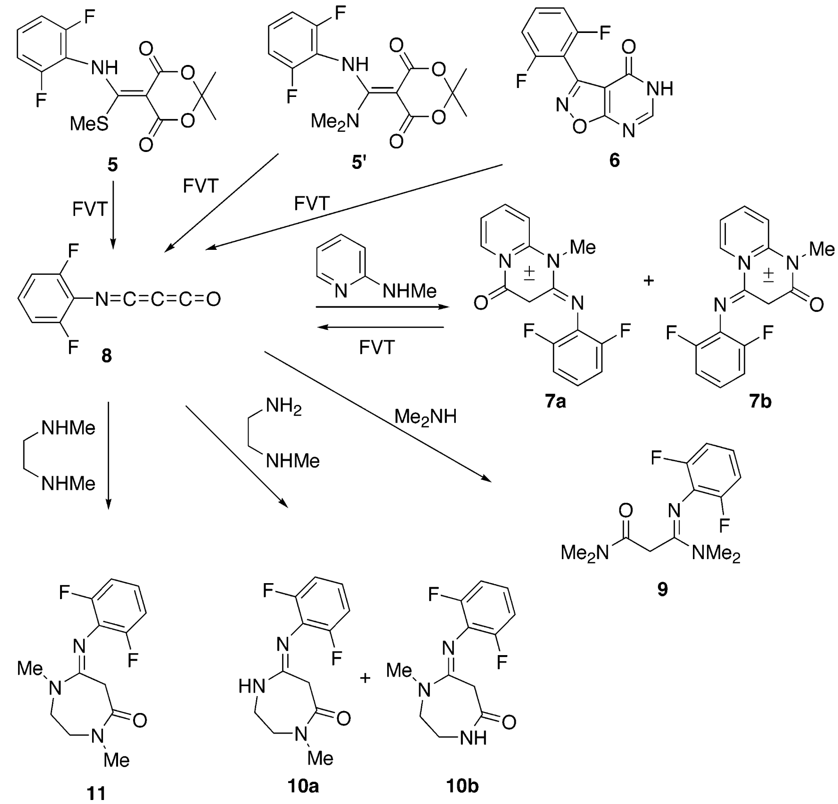
[1] Mosandl, T.; Kappe, C. O.; Flammang, R.; Wentrup, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1571−1573.

[2] Bibas, H.; Moloney, D. W. J.; Neumann, R.; Shtaiwi, M.; Bernhardt, P. V.; Wentrup, C. *J. Org. Chem.* **2002**, *67*, 2619−2631.

[3] (a) Taylor, E. C.; Garcia, E. J. *J. Org. Chem.* **1964**, *29*, 2116. (b) Rajagopalan, P.; Talaty, C. N. *Tetrahedron* **1967**, *23*, 3541.

10.1021/jo026275+ CCC: $22.00

SCHEME 1



from $CHCl_3$ and was characterized by X-ray crystallography. On FVT of the mixture of **7a** and **7b** at 550 °C, both isomers were fully converted to **8** (Scheme 1 and Figure 1).

Figure 1 shows the Ar matrix IR spectra obtained from the three precursors compared with the calculated spectrum at the B3LYP/6-31G** level of theory. It is clearly seen that the same compound is obtained in all cases, whereby the isoxazolopyrimidine (**6**) route is particularly useful because the few byproducts (HCN and HNCO) do not disturb the spectrum, and furthermore they are rather nonnucleophilic, so they do not impede the subsequent preparative reactions of the iminopropadienone. The mechanism of formation of RNCCCO from **6** is believed to involve breakage of the N−O bond to generate a putative vinylnitrene, which, when R = aryl, undergoes a 1,2-shift of R from C to N. The resulting ketenimine undergoes a cycloreversion to HCN, HNCO, and RNCCCO.[1]

The chemistry of **8** is unusual in several respects. The normal mode of reaction of iminopropadienones with bisnucleophiles is a rapid reaction with the strongest nucleophile at the highly electrophilic C=O group, followed by a slower reaction at the less electrophilic C=N group.[2] With mononucleophiles, this leads to malonic acid imide derivatives (e.g. **9**, Scheme 1, and **15**, Scheme 2), and with bis-nucleophiles, heterocyclic compounds are generated. In some cases minor amounts of the products of the opposite mode of addition are formed, corresponding to initial addition of the weaker nucleophile to the C=O group or initial addition of the stronger nucleophile to the C=N group, but the "normal" mode always dominates.[2,4] The formation of a 1:1 mixture of **7a** and **7b** is highly unusual and indicates that the electron-withdrawing effect of fluorine may have increased the electrophilicity of the C=N group in **8**. A similar phenomenon is observed in the reaction with the unsymmetrical *N*-methylethylenediamine to afford two perhydrodiazepinones, **10a** and **10b**, in a 1:1 ratio (Scheme 1). Naturally, the reaction with the symmetrical *N*,*N′*-dimethylethylenediamine afforded a single diazepinone, **11**.

The chemistry of the difluoro compound **8** is contrasted with that of the diethyl analogue **13** in Scheme 2. **13** Was obtained by FVT of the Meldrum's acid derivatives **12** and **12′**, themselves synthesized by reaction of 2,6-diethylphenyl isothiocyanate with Meldrum's acid, followed by *S*-methylation with methyl iodide and nucleophilic replacement of the methylthio group with dimethylamine. The iminopropadienone **13** was identified by its Ar matrix IR spectrum (Figure S1). Like **8**, **13** is not isolable at room temperature, and the preparative chemistry was performed as outlined above. Reaction with diethylamine gave the malonic imide derivative **15**. With 2-(methylamino)pyridine, only one product, **14**, corresponding to the "normal" mode of addition, was obtained. Also with *N*-methylethylenediamine, only one product, **16**, was obtained, corresponding to addition of the more nucleophilic NMe group to the C=O function. *N*,*N′*-dimethylethylenediamine afforded the diazepinone derivative **17**. Thus, the diethyl derivative **13** exhibits the

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[4] Andersen, H. G.; Mitschke, U.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 2*, **2001**, 602−607.

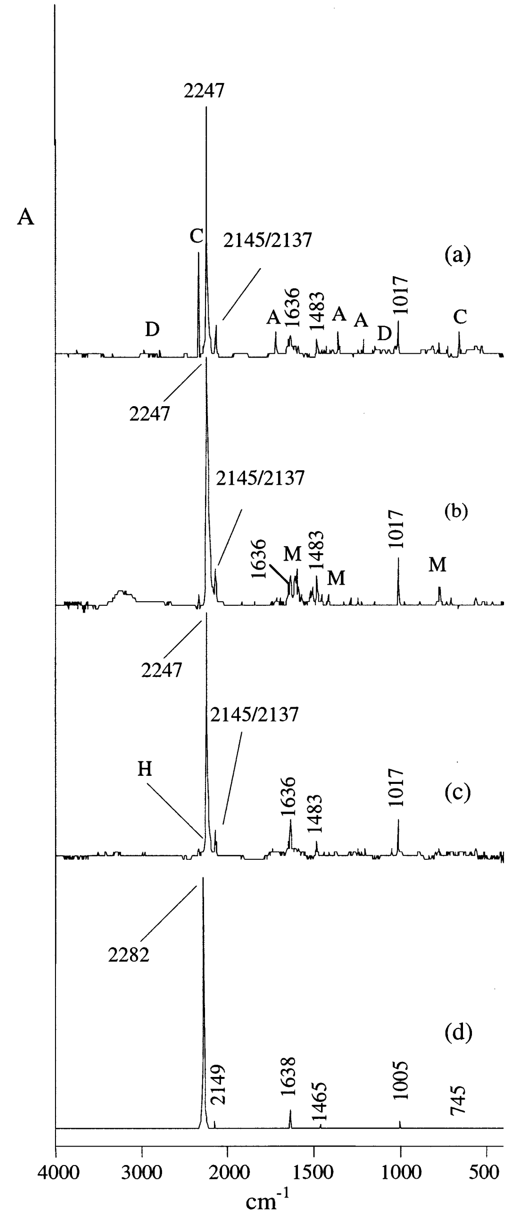
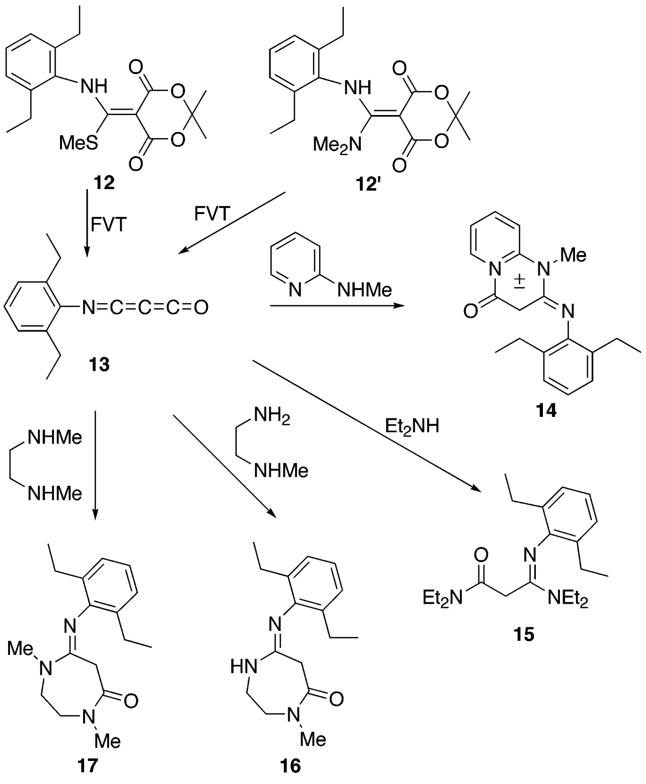


FIGURE 1. IR spectra of 2,6-diflourophenyliminopropadienone **8** (a) generated by FVT of dioxanedione **5′** (Ar matrix, 8 K), (b) by FVT of the 1:1 mixture of pyridopyrimidinium olates **7a** and **7b** (Ar matrix, 8 K), (c) by FVT of isoxazolopyrimidinone **6** (Ar matrix, 8 K), (d) DFT-calculated spectrum (B3LYP/6-31G**; scaling factor 0.9613). 2,6-Difluorophenyliminopropadienone **8:** 2247, 2145, 2137, 1636, 1483, 1017 cm^{-1}. (A) acetone: 1720, 1364, 1217, 1092 cm^{-1}. (C) carbon dioxide: 2345, 2340, 663 cm^{-1}. (D) dimethylamine: 2975, 2832, 1148 cm^{-1}. (M) 2-(methylamino)pyridine: 1612, 1602, 1578, 1524, 1511, 1421, 771 cm^{-1}. (H) HNCO: 2259 cm^{-1} (also present but not shown 3518, 3507, 770 cm^{-1}).

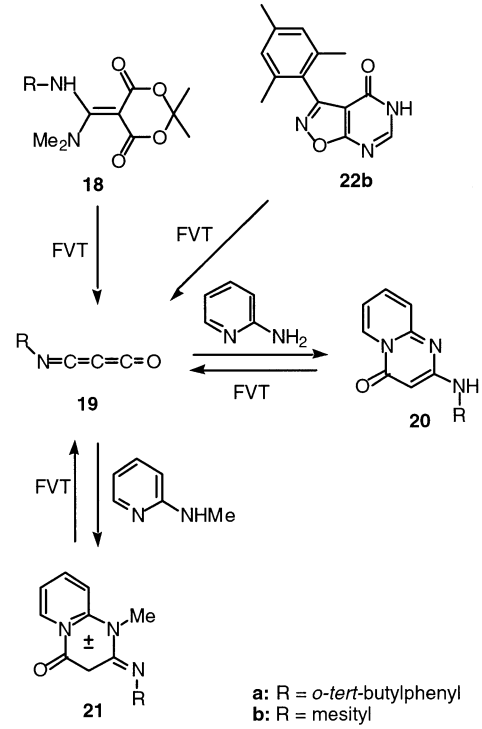
normal reactivity pattern similar to the neopentyl, the *o-tert*-butylphenyl (**19a**), and the mesityl (**19b**) derivatives.[2]

Compound **19a** was prepared by FVT of the Meldrum's acid derivative **18a** as previously described.[2] Reaction with 2-aminopyridine and 2-(methylamino)pyridine afforded the pyridopyrimidinone **20a** and the olate **21a**, respectively (Scheme 3). FVT of both **20a** and **21a** regenerated the iminopropadienone **19a** (Figure 2).

SCHEME 2

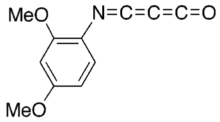


SCHEME 3



In the case of the mesityl derivative **19b**, obtained from the Meldrum's acid derivative **18b**, it has already been shown that the olate **21b** regenerates the iminopropadienone.[2] This also happens on FVT of the pyridopyrimidinone **20b** (Scheme 3 and Figure S2). Unlike the difluorophenyl case described above, the isoxazolopyrimidinone **22b** is not a good iminopropadienone precursor: while **19b** can be identified by its strong abosorption at 2240 cm^{-1}, the yield was low, and unidentified byproducts were formed.[5]

The 2,4- and 2,5-dimethoxyiminopropadienones 23 and **24** have also been prepared by FVT of the corresponding Meldrum's acid derivatives. The preparative procedures and matrix IR spectra are presented in the Supporting Information (Figures S3 and S4).



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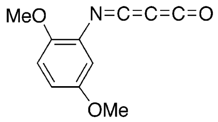

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Mechanism of Cleavage of Pyridopyrimidinones. What is the mechanism of formation of iminopropadienones from the neutral and mesoionic pyridopyrimidinones? It is known that 2-substituted pyridopyrimidin-4-ones of type **25** (X = Cl, MeS, or NMe_2) undergo elimination of HX under FVT conditions to generate 2-pyridyliminopropadienone **29**.[4,6] The reaction is believed to take place via the intermediates **26**−**28**, as indicated in Scheme 4. Why is this pathway not followed in the case of the pyridopyrimidinones **20**? An explanation is given in Scheme 4. In 2-aminopyridopyrimidinones **25**, where X = NHR, tautomerization can populate the mesoionic form **30**. This type of tautomerization is known for the corresponding hydroxy derivatives (i.e. **25**, X = OH).[7] It is also known that the non−mesoionic pyridopyrimidinones have somewhat lower energies than the mesoionic ones, but the difference is not large.[4] Ring opening[4,6,8] of mesoion **30** will lead to the transient ketene **31**, which can undergo a cycloelimination to 1*H*-2-iminopyridine **33** and the iminopropadienones **32** (**19**). Compound **33** tautomerizes to 2-aminopyridine.[9]

However, when X ≠ NHR or OH, tautomerization of 25 cannot take place, and the normal ring opening yields **26** and hence **27** and **28**, and 1,4-elimination leads to the observed product, 2-pyridyliminopropadienone **29**. We find that the meosionic 1-methylpyridopyrimidinones usually undergo cleavage to RNCCCO at FVT temperatures of ca. 350−550 °C. The nonmesoionic 2-aminopyridopyrimidinones require much higher temperatures, on the order of 800 °C. Thus, provided the initial barrier to tautomerization (**25** → **30**) can be overcome, the mesoionic pathway will dominate.

Thus, by proper choice of leaving group−secondary or tertiary amine−it is possible to synthesize a range of (substituted) phenyl- and pyridyliminopropadienones, and the pyridopyrimidionones **25** emerge as a very versatile group of precursors. This is particularly important, because it is not possible to obtain 2-pyridyliminopropadienones from Meldrum's acid precursors.[5,10]

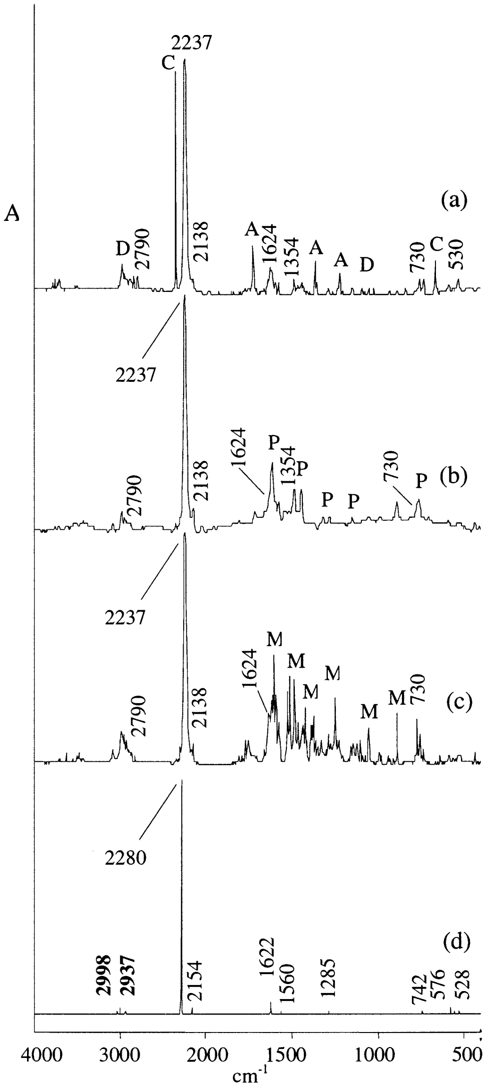

FIGURE 2. IR spectra of 2-*tert*-butylphenyliminopropadienone **19a** (a) generated by FVT of dioxanedione **18a** (Ar matrix, 8 K), (b) by FVT of pyridopyrimidinone **20a** (Ar matrix, 8 K), (c) by FVT of pyridopyrimidinium olate **21a** (Ar matrix, 8 K), and (d) DFT-calculated spectrum (B3LYP/6-31G**; scaling factor 0.9613). 2-*tert*-Butylphenyliminopropadienone **19a**: 2790, 2237, 2138, 1624, 1354, 730, 530 cm^{-1}. (A) acetone: 1720, 1364, 1217, 1092 cm^{-1}. (D) dimethylamine: 2975, 2832, 1148, 1021 cm^{-1}. (C) carbon dioxide: 2341, 663 cm^{-1}. (M) 2-(methylamino)pyridine: 1612, 1602, 1578, 1524, 1511, 1421, 771 cm^{-1}. (P) 2-aminopyridine: 1611, 1608, 1575, 1484, 1445, 1317, 1273, 1149, 735 cm^{-1}.

Conclusion

Meldrum's acid derivatives, isoxazolopyrimidinones, pyridopyrimidinones, and pyridopyrimidinium olates can all be used as precursors of iminopropadienones, RNCCCO. There are two mechanisms of fragmentation of pyridopyrimidinones **25**, which, by using either tertiary or secondary amine substituents, can be harnessed at will to produce either 2-pyridyliminopropadienone or aryliminopropadienones. 2,6-Difluorophenyliminopropadienone shows unusual reactivity, being indiscriminate in its reactions with nucleophiles at the C=O vs C=N bonds. The origin of this effect is the subject of an ongoing investigation.

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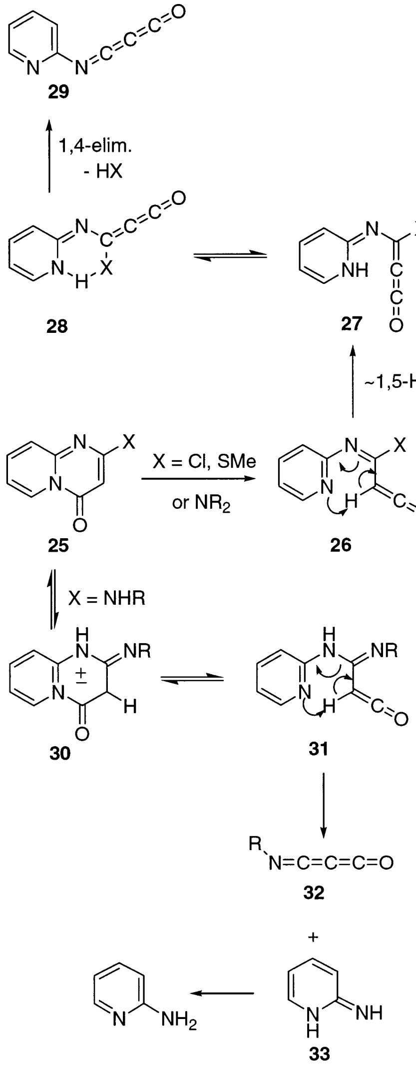
SCHEME 4



Experimental Section

The FVT apparatus and general equipment were as previously reported.[2,4]

Meldrum's Acid Route. 5-[(2,6-Difluoroanilino)(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione 5. A solution of 12.4 g (50 mmol) of 5-[bis(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione[11] and 7.1 g (55 mmol) of 2-*tert*-butylaniline in 100 mL of ethanol was refluxed for 24 h. The resulting solution was concentrated under reduced pressure, then 5 mL of *n*-hexane was added to precipitate white crystals, which were collected by filtration and recrystallized from hot THF to give 7.5 g (yield 45%) as colorless crystals: mp 145−146 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.78 (s, 6 H), 2.47 (s, 3 H), 7.02−7.37 (m, 2H), 7.34−7.43 (m, 1H), 12.2 (s, br, 1 H, NH); ^{13}C NMR (100 Hz, CDCl$_3$) δ 18.2 (SCH$_3$), 26.2, 87.4, 103.3, 111.8, 115.0, 129.8, 157.6 (dd, $J_{CF} = 252$ Hz), 163.5, 180.4. Anal. Calcd for $C_{18}H_{23}NO_4S$: C, 51.06; H, 3.98; N, 4.25. Found: C, 50.93; H, 4.04; N, 4.04.

5-[(2,6-Difluoroanilino)(dimethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione 5′ was prepared from compound **5** (10.0 g, 30.4 mmol) dissolved in 50 mL of THF, previously dried over sodium. A stream of gaseous dimethylamine was bubbled via a pipet through the stirred solution at such a slow rate that the gas just absorbed; the solution was then either heated at 50 °C for 24 h in a closed round-bottom flask or heated in a minireactor at 90 °C under high pressure (1000 psi) for 6 h. (**CAUTION**: The heating in a closed system or under pressure should be carried out in an apparatus equipped with a proper safety valve.) The resulting solution was concentrated by evaporating some of the solvent to precipitate white crystals, which were collected by filtration and recrystallized from hot THF to give 6.9 g (yield 70%) in the first case and 8.8 g (yield 90%) in the second case as colorless crystals: mp 186−188 °C; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 1.67$ (s, 6 H), 2.89 (s, 6 H), 6.96 (t,$^3J = 8.4$ Hz, 2H), 7.17−7.22 (m, 1H) 9.23 (s, br, 1 H, NH); ^{13}C NMR (100 Hz,CDCl$_3$) δ 26.2, 41.4, 76.2, 102.3, 112.1, 116.7, 127.7, 157.3 (dd, $J_{CF} =$ 252 Hz), 164.3, 165.2. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 55.21; H, 4.94; N, 8.59. Found: C, 55.11; H, 5.00; N, 8.55.

2,6-Diethylphenyl isothiocyanate was prepared by the procedure of Habib et al.[12] with modifications. 2,6-Diethylaniline (15.0 g, 100 mmol) and phenyl isothiocyanate (29.7 g, 220 mmol) were heated under reflux for 24 h, whereupon a white flaky crystalline sublimate of diphenylthiourea appeared in the condenser. The mixture was cooled, quenched with 100 mL of petroleum spirit (bp 60−90 °C), filtered, and the filtrate was evaporated to dryness. The product was purified by vacuum distillation (1×10^{-4} mbar) to afford 17.2 g of colorless oil (90%): bp 178 °C; IR (KBr) ν 3064, 2087, 1801, 1593 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.44 (t, $^3J = 7.5$ Hz, 6H), 2.90 (q, $^3J = 7.5$ Hz, 4H), 7.22−7.38 (m, 3H); ^{13}C NMR (50 Hz, CDCl$_3$) δ 14.2, 25.6, 126.4, 127.3, 128.1, 134.9, 140.8.

5-[(2,6-Diethylanilino)(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6 -dione 12. A solution of 14.4 g (100 mmol) of isopropylidene malonate (Meldrum's acid) and 28 mL triethylamine (200 mmol) in 70 mL of dry acetonitrile was stirred for 30 min, then 19.1 g (100 mmol) of 2,6-diethylphenyl isothiocyanate was added, and the mixture was heated at 60 °C for 12 h. A total of 7.0 mL (100 mmol) of idomethane was added dropwise to the mixture at room temperature and the resulting solution was then stirred for 48 h. The resulting solution was concentrated under reduced pressure, then 5 mL of *n*-hexane was added to precipitate yellow crystals, which were collected by filtration and recrystallized from hot THF to give 21.0 g (yield 60%) as pale yellow crystals: mp 150−151 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.19 (t, $^3J = 7.6$ Hz, 6H, CH_3CH$_2$), 1.75 (s, 6 H, CMe$_2$), 2.35 (s, 3 H, SCH$_3$), 2.49−2.62 (m, 4H, CH$_3$CH_2), 7.17 (d, $^3J = 7.9$ Hz, 2H), 7.31 (t, $^3J = 7.6$ Hz, 1H), 12.2 (s, br, 1H, NH). ^{13}C NMR (100 Hz,CDCl$_3$) δ 14.2 (CH$_3$CH$_2$), 18.3 (SCH$_3$), 24.6 (CH$_3$$CH_2$), 26.2 (C$Me_2$), 84.1 (C=$C$CO), 102.9 ($CMe_2$), 126.6, 129.3, 134.0, 140.8, 163.9(CO), 180.1 (C=C−CO) (the assignment of the peaks was supported by HSQC and HMBC experiments). Anal. Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 61.78; H, 6.69; N, 3.96.

5-[(2,6-Diethylanilino)(dimethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione 12′ was prepared from **12** (12.2 g, 35 mmol) as described for **5′** above to give 8.5 g (yield 70%) by the first method and 10.9 g (yield 90%) by the second method as colorless crystals: mp 199−200 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.18 (t, $^3J = 7.7$ Hz, 6H), 1.73 (s, 6 H), 2.40−2.63 (m, 4H), 2.66 (s, 6 H), 7.12 (d, $^3J = 7.4$ Hz, 2H), 7.21(t, $^3J = 7.4$ Hz, 1H), 9.65 (s, br, 1H, NH); ^{13}C NMR (100 Hz,CDCl$_3$) δ 14.0, 24.3, 26.1, 41.2, 75.3, 102.0, 126.6, 127.9, 135.1, 140.1, 164.6, 164.8. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.71; H, 7.78; N, 7.94.

FVT with Argon Matrix Isolation. 2,6-Difluorophenyliminopropadienone 8. 5-[(2,6-Difluoroanilino)(dimethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione 5′ (10 mg, 0.03 mmol) was sublimed at 70 °C through the FVT tube at 400−700 °C with Ar matrix isolation of **8** on a BaF$_2$ disk at 8 K over the course of 30 min: IR (Ar, 8 K) 2790 w, 2247 vs, 2145 w, 2137 w, 1636 m, 1483 w, 1017 w, 778 w cm^{-1}. Also present were the following peaks: 1768 w, 1722 m, 1362 m, 1218 m, 1092 m cm^{-1} (acetone); 2976 w, 2831 w, 1483 w,

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1148 w, 1021 w cm^{-1} (dimethylamine); 2346, 2340, 664 m cm^{-1} (carbon dioxide).

2,6-Diethylphenyliminopropadienone 13. 5-[(2,6-Diethylanilino)(dimethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **12′** (10 mg, 0.03 mmol) was sublimed at 85 °C through the FVT tube at 400−700 °C with Ar matrix isolation of **13** on a BaF$_2$ disk at 8 K over the course of 30 min:

IR (Ar, 8 K) 2943 w, 2791 w, 2244 vs, 1627 m, 1354 w, 731 m cm^{-1}; peaks due to acetone, dimethylamine, and carbon dioxide were also present (see above).

Neat Film IR Spectra. 2,6-Difluorophenyliminopropadienone 8. Compound **5′** (10 mg, 0.03 mmol) was sublimed at 70 °C through the FVT tube at 700 °C (the system was operated at a vacuum of 2×10^{-5}), and **8** was collected as a neat film on a BaF$_2$ disk cooled to 50 K over the course of 15 min: IR (neat) 2224 vs, 1610 m, 754 w, 534 w cm^{-1}. Also present were the following peaks: 1710 m, 1365 m, 1227 m cm^{-1} (acetone); 2967 w, 2822 w, 1483 w, 1143 w cm^{-1} (dimethylamine); 2341, 2338 cm^{-1} (carbon dioxide).

2,6-Diethylphenyliminopropadienone 13. Compound **12′** (10 mg, 0.03 mmol) was sublimed at 85 °C through the FVT tube at 700 °C, and **13** was collected as a neat film at 50 K as above: IR (neat) 2224 vs, 1610 m, 754 w, 534 w cm^{-1}; peaks due to acetone, dimethylamine, and carbon dioxide were also present (see above).

Preparative Pyrolysis Experiments. Standard Procedure for Synthesis and Preparative Trapping of Aryliminopropadienones. 5-[Arylamino)(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **5** or **12** or 5-[(arylamino)(dimethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **5′** or **12′** (1.0 mmol) was sublimed at 150−180 °C/10^{-4} mbar and thermolyzed at 700 °C over the course of 3 h; the iminopropadienones **8** and **13** were collected on a coldfinger cooled to ca. −196 °C using liquid nitrogen and connected to an oil diffusion vacuum pump. Upon completion of the thermolysis, the pump was closed, the pressure was equalized with N$_2$, and an excess or 1 equiv of trapping agent in 15−30 mL of dry ether, THF, or dichloromethane was injected onto the thermolysate. This coldfinger was then allowed to warm to room temperature. The following compounds were prepared.

3-Dimethylamino-3-[(2,6-difluorophenyl)]imino-*N*,*N*-dimethylpropanamide 9. Excess dimethylamine as a solution in ether (20 mL) was injected on the coldfinger containing **8** as described above, and the resulting mixture was stirred for 12 h. The crude product was purified by flash chromatography (silica gel, 5% MeOH in ether) to yield 100 mg (37%) of a yellow oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.64 (s, 3H), 2.80 (s, 3H), 3.06 (s, 6H), 3.28 (s, 2H), 6.83−6.93 (m, 3H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 34.3, 35.6, 36.6, 39.6, 111.5, 116.0, 125.9, 156.2 (dd, J_{CF} = 252 Hz), 158.8, 165.8. Anal. Calcd for C$_{13}$H$_{17}$F$_2$N$_3$O: C, 57.98; H, 6.36; N, 15.60. Found: C, 57.59; H, 6.35; N; 15.40.

1-Methyl-2-[(2,6-difluorophenyl)imino]-1,2-dihydropyrido[1,2-*a*]pyrimidin-1-ium-4-olate 7a and 1-Methyl-4-[(2,6-difluorophenyl)imino]-1,2-dihydropyrido[1,2-a]pyrimidin-1-ium-2-olate 7b. 2-(Methylamino)pyridine (119 mg; 1.1 mmol) in 15 mL of dry THF was injected onto the coldfinger covered with iminopropadienone **8** obtained from Meldrum's acid derivative **5** (329 mg, 1.0 mmol), and the resulting mixture was stirred for 24 h. The solvent was evaporated, and the crude product was purified by flash chromatography (silica gel, 50% MeOH/ether) to afford 150 mg (yield 52%) of **7a**/**7b** in a 1:1 ratio as a yellow solid (mp 180−185 °C). Compound **7a** crystallized from the CDCl$_3$ solution in the NMR tube after prolonged storing at room temperature: mp 208−209 °C. X-ray data for this compound are given in the Supporting Information (Figure S5 and Tables S1−S5). The following data are for the mixture of **7a** and **7b**: IR (KBr) ν 1717, 1665, 1623 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.67 (s, 3H), 3.92 (s, 3H), 4.89 (s, 1H), 4.93 (s, 1H), 6.87−6.93 (m, 6H), 7.22 (td, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H), 7.31 (td, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H), 7.42 (t, ^3J = 7.4 Hz, 2H), 8.03−8.12 (m, 2H), 9.28 (dd, ^3J = 6.8 Hz, ^4J = 1.8 Hz, 1H), 10.0 (dd, ^3J = 7.0 Hz, ^4J = 1.2 Hz, 1H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 29.4, 31.4, 77.1, 78.4, 111.5, 111.7, 112.7, 113.1, 114.6, 115.0, 121.7, 122.1, 126.6, 127, 132.1, 133.1, 142.3, 142.9, 147.3, 147.4, 149.1, 152.8, 155.8 (dd, J_{CF} = 244 Hz), 156.2 (C−F, dd, J_{CF} = 244 Hz). Anal. Calcd for C$_{15}$H$_{11}$F$_2$N$_3$O: C, 62.72; H, 3.86; N, 14.63. Found: C, 62.50; H, 4.00; N, 14.50.

4-Methyl-7-[(2,6-difluorophenyl)imino]perhydro[1,4]diazepin-5-one 10a and 1-Methyl-7-[(2,6-difluorophenyl)imino]perhydro[1,4]diazepin-5-one 10b. To iminopropadienone **8**, obtained from Meldrum's acid derivative **5** (329 mg, 1.0 mmol), was injected a solution of 81.5 mg (1.1 mmol) of *N*-methylethylenediamine in 30 mL of dry THF, and the resulting mixture was stirred for 3 days. The solvent was evaporated, and the crude product was purified by flash chromatography (silica gel, 5% MeOH/ether) to yield 75 mg (30%) of **10a**/**10b** in a 1:1 ratio as a yellow oil: IR (KBr) ν 3255, 1661, 1645, 1617 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.00 (s, 3 H), 3.21 (s, 3 H), 3.41 (s, 2 H,), 3.47 (s, 2 H), 3.48−3.50 (m, 2H), 3.59−3.63 (m, 4H), 3.74−3.77 (m, 2H), 3.86 (br, 1H), 6.38 (br, 1H), 6.83−6.91 (m, 6H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 35.9, 37.3, 38.0, 41.4, 42.7, 47.5, 49.6, 51.6, 110.4 (m), 111.3 (m), 122.0 (t), 122.5(t), 127.2 (t), 127.8 (t), 154.2, 155.1 (dd, J $_{CF}$ = 241 Hz), 155.2 (dd, J_{CF} = 242 Hz), 155.8, 165.0, 167.0. HRMS calcd for C$_{12}$H$_{13}$F$_2$N$_3$O 253.1027, found 253.1021. Anal. Calcd for C$_{12}$H$_{13}$F$_2$N$_3$O: C, 56.91; H, 5.17; N, 16.59 Found: C, 57.12; H, 5.29; N, 16.40

1,4-Dimethyl-7-[(2,6-difluorophenyl)imino]perhydro-[1,4]diazepin-5-one 11. To iminopropadienone **8**, obtained from Meldrum's acid derivative **5** (329 mg, 1.0 mmol), was injected a solution of 97.0 mg (1.1 mmol) of *N*,*N*′-dimethylethylenediamine in 30 mL of dry THF, and the resulting mixture was stirred for 3 d. The solvent was evaporated, and the crude product was purified by flash chromatography (silica gel, 5% MeOH/ether), to yield 110 mg (41%) as a yellow oil: IR (KBr) ν 1663, 1634 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.97 (s, 3 H), 3.20 (s, 3 H), 3.52 (s, 2 H), 3.53−3.54 (m, 2H), 3.73−3.76 (m, 2H), 6.85−6.87 (m, 3H); ^{13}C NMR (50 Hz, CDCl$_3$) δ 35.8, 37.1, 38.0, 49.4, 50.4, 111.3 (m), 122.0 (t), 127.2 (t), 155.2 (dd, J_{CF} = 256 Hz), 156.3, 164.9. Anal. Calcd for C$_{13}$H$_{15}$F$_2$N$_3$O: C, 58.43; H, 5.62; N, 15.73. Found: C, 58.49; H, 5.59; N, 15.40.

1-Methyl-2-[(2,6-diethylphenyl)imino]-1,2-dihydropyrido[1,2-*a*]pyrimidin-1-ium-4-olate 14. 2-(Methylamino)pyridine (119 mg, 1.1 mmol) in 15 mL of dry CH$_2$Cl$_2$ was injected onto the coldfinger containing **13** (obtained from Meldrum's acid derivative **12** (349 mg, 1.0 mmol) as described above), and the resulting mixture was stirred for 24 h. The solvent was evaporated, and the crude product was purified by flash chromatography (silica gel, 50% MeOH/ether) to 180 mg (yield 59%) of a yellow solid: mp 157−158 °C; IR (KBr) ν 1717, 1636, 1617, 1559 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.12 (t, ^3J = 7.7 Hz, 6H) 2.38−2.48 (m, 4H), 3.90 (s, 3H), 4.62 (s, 1H), 6.94 (t, ^3J = 7.4 Hz, 1H), 7.03 (d, ^3J = 7.3 Hz, 2H), 7.13 (t, ^3J = 7.0 Hz, 1H), 7.39 (d, ^3J = 8.8 Hz, 1H), 8.00 (td, ^3J = 7.0 Hz, ^4J = 1.5 Hz, 1H), 9.23 (dd, ^3J = 6.6 Hz, ^4J = 1.5 Hz, 1H); ^{13}C NMR (100 Hz,CDCl$_3$) δ 14.1, 24.5, 31.4, 67.4, 112.7, 114.2, 122.7, 126.0, 132.0, 135.0, 142.8, 144.8, 148.3, 149.3, 151.3. Anal. Calcd for C$_{19}$H$_{21}$N$_3$O: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.50; H, 6.91; N, 13.67.

Diethyl 3-Diethylamino-3-(2,6-diethylphenyl) Iminopropanamide 15. Diethylamine (0.21 mL, 2.0 mmol) in 15 mL of dry CH$_2$Cl$_2$ was injected onto the coldfinger containing **13** obtained from **12** as above, and the resulting mixture was stirred for 12 h. The crude product was purified by flash chromatography (silica gel, 3% MeOH in ether) to yield 200 mg (58%) of a white solid: mp 92−93 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.70 (t, ^3J = 7.2 Hz, 3H), 0.99 (t, ^3J = 7.2 Hz, 3H), 1.12 (t, ^3J = 7.2 Hz, 6H), 1.22 (t, ^3J = 7.2 Hz, 6H), 2.47−2.53 (m, 4H), 2.64 (q, ^3J = 7.2 Hz, 2H), 3.08 (s, 2H), 3.19 (q, ^3J = 6.6 Hz, 2H), 3.46−3.51 (m, 4H), 6.83 (t, ^3J = 7.5 Hz, 1H), 6.96 (d, ^3J = 7.5 Hz, 2H). ^{13}C NMR (100 Hz, CDCl$_3$) δ 12.9, 13.0, 13.6, 13.7, 24.3, 32.2, 40.8, 42.1, 42.5, 125.6, 127.6, 135.9 141.9, 153.1, 165.1. Anal. Calcd for $C_{21}H_{35}N_3O$: C, 73.00; H, 10.21; N, 12.16. Found: C, 73.05; H, 10.01; N, 12.11.

4-Methyl-7-[(2,6-diethylphenyl)imino]perhydro[1,4]diazepin-5-one 16. To iminopropadienone **13**, obtained from **12** as above, was injected a solution of 81.5 mg (1.1 mmol) of *N*-methylethylenediamine in 30 mL of dry THF, and the resulting mixture was stirred for 3 days. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, 5% MeOH/ether) to yield 70 mg (26%) as a yellow oil: IR (KBr) ν 3340, 1646 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.13 (t, ^3J = 7.7 Hz, 6H), 2.37−2.47 (m, 4H), 3.01 (s, 3 H), 3.43−3.71 (m, 4H), 3.82 (s, 2 H), 4.50 (br, 1H), 6.97(t, ^3J = 7.0 Hz, 1H), 7.06 (d, ^3J = 0.0 Hz, 2H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 14.0, 24.5, 35, 41.4, 43.8, 52.2, 123.2, 126.3, 134.7, 144.3, 150.9, 167.7. HRMS calcd for $C_{16}H_{23}N_3O$ 273.1841, found 273.1840. Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.48; N, 15.37 Found: C, 70.21; H, 8.24; N, 15.20

1,4-Dimethyl-7-[(2,6-diethylphenyl)imino]perhydro-[1,4]diazepin-5-one 17. To iminopropadienone **13**, obtained from **12** as above, was injected a solution of 97.0 mg (1.1 mmol) *N,N′*-dimethylethylenediamine in 30 mL of dry THF, and the resulting mixture was stirred for 3 d. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, 5% MeOH/ether), to yield 150 mg (yield 52%) as a white crystals: mp 125−126 °C; IR (KBr) ν 1627, 1586 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.11 (t, ^3J = 7.6 Hz, 6H), 2.20−2.42 (m, 4H), 2.96 (s, 3 H), 3.14 (s, 3 H), 3.31 (s, 2 H), 3.52−3.56 (m, 2H), 3.64−3.70 (m, 2H), 6.86−6.94 (m, 1H), 7.00−7.04 (m, 2H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 13.6, 24.4, 35.6, 37.2, 37.9, 49.8, 50.2, 122.4, 125.6, 133.9, 146.1, 151.9, 165.9. Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.04; H, 8.77; N, 14.62. Found: C, 69.95; H, 8.74; N, 14.40.

Isoxazolopyrimidinone Route. 2,6-Difluorophenylcarbaldoxime. A solution of 19.6 g (0.14 mol) of 2,6-difluorobenzaldyhyde in 200 mL of ethanol was added under vigorous stirring at 60 °C to a 1 L aqueous solution of 15.0 g (0.16 mol) of sodium acetate and 11.0 g (0.16 mol) of hydroxylamine hydrochloride. The mixture was refluxed for 6 h and then cooled in a refrigerator overnight to precipitate 13.3 g of fine, long white crystals (yield 60.5%): mp 114−116 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.87−6.93 (m, 2 H), 7.20−7.7.30 (m, 1H), 8.27 (s, 1 H), 10.1 (s, 1 H); ^{13}C NMR (100 Hz, CDCl$_3$) δ 109.6 (t), 112.0 (m), 131.0 (t), 140.4, 157.6 (dd, J_{CF} = 256 Hz).

2,6-Difluorobenzhydroximoyl chloride was prepared by the method of Coda and Tacconi.[13] A solution consisting 13.12 g (0.08 mol) of 2,6-difluorophenylcarbaldoxime, 130 mL of HCl (32%), and 100 mL of glacial acetic acid was stirred for 1 h and then cooled in an ice bath to reach 0 °C. Sodium hypochlorite (0.11 mol as 66 mL of a 12.5% w/v solution in water) was added dropwise using a dropping funnel to afford a milky solution. The mixture was left stirring overnight and then refrigerated to yield 8.5 g of a white precipitate (55.4%): mp 104−106 °C; ^{1}H NMR (400 MHz, MeOD) δ7.22−7.29 (m, 2 H), 7.59−7.67 (m, 1H); ^{13}C NMR (100 Hz, MeOD) δ 111.7 (t), 112.3 (m), 126.1, 133.3 (t), 159.6 (dd, J_{CF} = 256 Hz).

5-Amino-2,6-difluorophenyl-4-isoxazolecarboxamide was prepared by the method of Rajagopalan and Talaty.[3b] 2-Cyanoacetamide (1.68 g, 20.0 mmol) in 30 mL of absolute ethanol was added into a well-stirred solution of sodium ethoxide, which was prepared from 0.46 g (20.0 mmol) of sodium in 30 mL of absolute ethanol. The resulting suspension was stirred at 0 °C in an ice bath. 2,6-Difluorobenzhydroximoyl chloride (3.8 g; 20.0 mmol) in 30 mL of absolute ethanol was added slowly to the mixture, which was stirred for 15 min at 0 °C and then allowed to stir for another 90 min at room temperature. The mixture was then refluxed for 2.5 h and later hydrolyzed by pouring it onto 25 mL of crushed ice. The precipitate was filtered off and recrystallized from methanol/water to afford 1.3 g (27%): mp 174−176 °C; ^{1}H NMR (200 MHz, MeOD) δ 5.02 (s, 2H), 6.42 (s, 2H), 7.05−7.7.28 (m, 2 H), 7.53−7.65 (m, 1H); ^{13}C NMR (100 Hz, MeOD) δ 88.5, 106.7 (t), 112.0 (m), 132.7 (t), 151.1, 159.9 (dd, J_{CF} = 250 Hz), 163.3, 170.8.

3-(2,6-Diflourophenyl)isoxazolo[5,4-*d*]pyrimidine-4(5*H*)-one 6 was prepared by adaptation of the method of Taylor and Garcia.[3a] The foregoing isoxazolecarboxamide (2.12 g, 8.8 mmol) and 15 g (100 mmol) of triethyl orthoformate were dissolved in 28 mL of acetic anhydride and heated under reflux for 24 h. The mixture was evaporated and ethanol was added to the residue. 15 mL of *n*-hexane was added, the solution turned cloudy. The mixture was filtered off after it was frozen for 4 days at −20 °C to yield 1.3 g (60%): mp 258−260 °C; IR (KBr) 3445, 1761, 1633 cm^{-1}; ^{1}H NMR (200 MHz, MeOD) 7.16−7.28 (m, 2 H), 7.60−7.75 (m, 1H), 8.36 (s, 1H); ^{13}C NMR (100 Hz, MeOD) 103.7, 106.7 (t), 113.0 (m), 134.4 (t), 151.3, 153.3, 158.8, 161.9 (dd, J_{CF} = 253 Hz), 177.3. Anal. Calcd for $C_{11}H_5F_2N_3O_2$: C, 53.02; H, 2.02; N, 16.86. Found: C, 53.32; H, 2.09; N, 16.60.

Matrix Isolation of 2,6-Difluorophenyliminopropadienone 8 Generated from 6. 3-(2,6-Difluorophenyl)isoxazolo-[5,4-*d*]pyrimidine-4(5*H*)-one **6** (10 mg, 0.04 mmol) was sublimed at 100 °C through the FVT tube at 700 °C with Ar matrix isolation of **8** on a BaF$_2$ disk at 8 K over the course of 20 min: IR (Ar, 8 K) 2247 vs, 2145 w, 2137 w, 1636 m, 1483 w, 1017 m, 778 w cm^{-1}. Also present were the following peaks: 3518 w, 3507 w, 2259 m, 770 w cm^{-1} (hydrogen isocyanate, HNCO).

FVT of Pyridopyrimidinones. 2-*tert*-Butylphenyliminopropadienone 19a Generated from 2-[(2-*tert*-Butylphenyl)amino]pyrido[1,2-a]pyrimidin-4-one 20a. Compound **20a**[2] (10 mg, 0.025 mmol) was sublimed at 140 °C through the FVT tube at 850 °C with Ar matrix isolation of **19a** on a BaF$_2$ disk at 8 K over the course of 10 min: IR (Ar, 8 K) 2237 vs, 2138 w, 1624 m, 1354 w, 730 w cm^{-1}. Also present were the following peaks: 3535 w, 3429 w, 3074 w, 1611 s, 1608 s, 1575 w, 1484 m, 1445 m, 1317 w, 1273 w, 1149 w, 735 m cm^{-1} (2-aminopyridine).

Mesityliminopropadienone 19b Generated from (2-Mesitylamino]pyrido[1,2-a]pyrimidin-4-one 20b. Compound **20b**[2] (10 mg, 0.025 mmol) was sublimed at 140 °C through the FVT tube at 850 °C with Ar matrix isolation of **19b** on a BaF$_2$ disk at 8 K over the course of 10 min: IR (Ar, 8 K) 2240 vs, 1627 m, 1583 w, 1480 m, 1092 w, 730 w cm^{-1}; peaks due to 2-aminopyridine were also present (see above).

FVT of Pyridopyrimidinium Olates. 2,6-Difluorophenyliminopropadienone 8 Generated from 1-Methyl-2-[(2,6-difluorophenyl)imino]-1,2-dihydropyrido[1,2-a]pyrimidin-1-i um-4-olate 7a and 1-Methyl-4-[(2,6-difluorophenyl)imino]-1,2-dihydropyrido[1,2-a]pyrimidin-1-i um-2-olate 7b. The 1:1 mixture of compounds **7a** and **7b** (10 mg, 0.031 mmol) was sublimed at 160 °C through the FVT tube at 550 °C with Ar matrix isolation of **8** on a BaF$_2$ disk at 8 K over the course of 10 min: IR (Ar, 8 K) 2247 vs, 2145 w, 2137 w, 1636 m, 1483 w, 1017 w cm^{-1}. Also present were the following peaks: 1612 s, 1602 s, 1578 w, 1524 m, 1511 m, 1459 m, 1421 m, 1336 m, 1329 m, 1289 m, 1156 m, 1074 m, 771 m, 734 w cm^{-1} [2-(methylamino)pyridine].

2-*tert*-Butylphenyliminopropadienone 19a Generated from 1-Methyl-2-[(2-*tert*-butylphenyl)imino]-1,2-dihydropyrido[1,2-a]pyrimidin-1-ium-4-olate 21a. Compound ***21a***[2] (10 mg, 0.031 mmol) was sublimed at 160 °C through the FVT tube at 550 °C with Ar matrix isolation of ***19a*** on a BaF$_2$ disk at 8 K over the course of 10 min: IR (Ar, 8 K) 2237 vs, 2138 w, 1624 m, 1354 w, 730 w cm^{-1}; peaks due to 2-(methylamino)pyridine were also present (see above).

Reference Spectra. 2-Aminopyridine: IR (Ar, 8 K) ν 3535 m, 3429 m, 3074 w, 3031 w, 1611 vs, 1608 vs, 1586 w, 1575 m, 1497 w, 1484 s, 1445 s, 1317 m, 1273 w, 1149 w, 987 w, 846 w, 803 w, 785 w, 772 w, 765 w, 735 w, 519 w cm^{-1}. Sublimation temperature 20 °C.

2-(Methylamino)pyridine: IR (Ar, 8 K) ν 3503 w, 3481 w, 2821 w, 1612 s, 1606 s, 1602 vs, 1578 m, 1574 m, 1524 s,

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[13] Coda, A. C.; Tacconi, G. *Gazz. Chim. Ital.* **1984**, *114*, 131.

1511 s, 1493 w, 1464 w, 1459 m, 1440 w, 1429 w, 1421 s, 1414 m, 1336 m, 1329 w, 1289 m, 1169 w, 1156 w, 1149 w, 1131 w, 1089 w, 1074 w, 981 w, 771 s, 734 w, 522 w cm^{-1}. Sublimation temperature 10 °C.

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Supporting Information Available: Experimental procedures for the preparation of the dimethoxyphenyliminopropadienones; IR spectra of diethyliminopropadienone [Ar matrix and calculated (B3LYP/6-31G**), Figure S1], mesityliminopropadienone (Ar matrixes, Figure S2), and dimethoxyphenyliminopropadienones (Ar matrixes and neat films, Figures S3−S4); X-ray data for pyridopyrimidinium olate **7a** (Figure S5 and Tables S1−S5); Cartesian coordinates, energies, and calculated IR spectra of **8**, **13**, **19a**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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