SYNTHESIS OF 3-(4-ARYL-3-CYANO-2-METHOXYPYRIDIN-6-YL)TROPOLONES BY THE REACTIONS OF 3-CINNAMOYLTROPOLONES WITH MALONONITRILE

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Abstract - 3-Cinnamoyltropolones (**1a-k**) reacted with malononitrile in methanol in the presence of sodium hydroxide or methoxide to give 2-(4-aryl-3-cyano-2-methoxypyridin-6-yl)tropolones (**2a-k**) *via* Michael addition and cyclization. The reactions in the presence of ethoxide or 1-propoxide afforded the corresponding 2-ethoxy- and 2-(1-propoxy)pyridine derivatives (**3a,b**), respecvely. 3-(3-Heterocycle-substituted 2-propenoyl)tropolones (**6a-d**) gave the pyridines (**7a-d**) having both tropolone and heteocyclic ring.

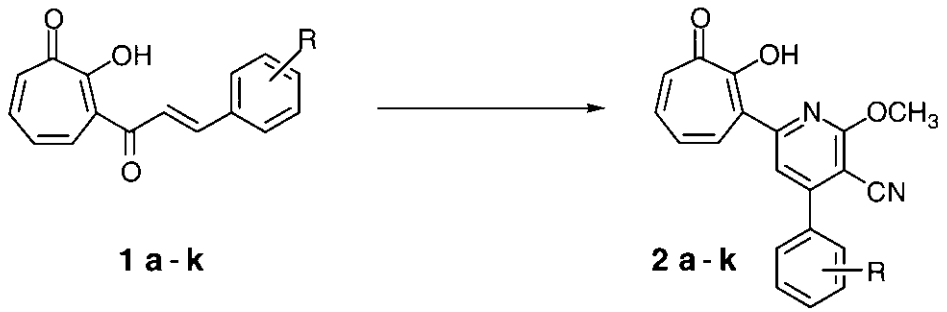
The troponoid system is included in many natural products as alkaloids and antibiotics. Their discovery attracted pharmacological interest.[1] In addition, interest in the synthesis of multicyclic pyridine-containing compounds has increased in recent years because of their biological and pharmacological activities.[2,3] The synthesis of phenyl-substituted pyridines has been widely investigated.[4] Recently, several synthetic methods *via* condensation and cyclization were reported such as the reaction of α,β-unsaturated ketones with *N*-(1-phenylvinyl)iminophosphorane,[5] the reaction of aromatic aldehydes and alkyl ketones with malononitrile in the presence of ammonium acetate,[6] and the reaction of chalcones with malononitrile in the presence of sodium hydroxide.[7,8]

In an extension of our syntheses of heterocycle-substituted tropolones such as 3-(3-pyrazolyl)tropolones,[9] 3-(5-isoxazolyl)tropolones,[9] 3-(4-thiazolyl)tropolones,[10,11] and 3-(2-quinolyl)tropolones,[12] the present paper describe the synthesis of pyridine derivatives having two different aromatic rings, tropolone and benzene rings, by the reaction of 3-cinnamoyltropolones[13,14] with malononitrile in the presence of sodium hydroxide or alkoxide.

RESULTS AND DISCUSSION

Reaction of 3-Cinnamoyltropolones (1a-k) with Malononitrile. To a solution of 3-(4-methylcinnamoyl)tropolone (**1b**) and two molar amounts of malononitrile in methanol was added two molar

equivalents of sodium hydroxide. The mixture was stirred for 24 h at room temperature and neutralized with acetic acid to afford 3-[3-cyano-2-methoxy-4-(4-methylphenyl)pyridin-6-yl]tropolone (**2b**) in 53% yield. Instead of sodium hydroxide, the reaction using sodium methoxide gave the same product (**2b**) in 53% yield. When the reaction was carried out in the presence of an equimolar amount of sodium hydroxide, the cinnamoyltropolone (**1b**) was recovered quantitatively. This means that an equimolar amount of the base was consumed for salt formation with an acidic tropolone (**1b**). Thus, it was revealed that it is necessary to use two molar equivalents of base.

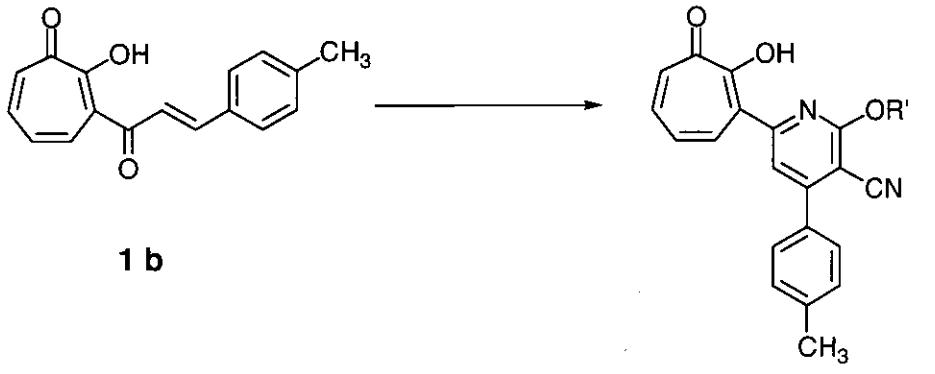


1 a - k **2 a - k**

a	R = H	**g**	R = 3,4-$(OCH_3)_2$
b	R = 4-CH_3	**h**	R = 2,3,4-$(OCH_3)_3$
c	R = 2-OCH_3	**i**	R = 3,4-(OCH_2O)
d	R = 3-OCH_3	**j**	R = 4-Cl
e	R = 4-OCH_3	**k**	R = 4-NO_2
f	R = 2,4-$(OCH_3)_2$		

Scheme 1

In a similar manner, the reactions of eight 3-cinnamoyltropolones (**1a,c-i**) were also carried out at room temperature using two molar equivalents of sodium hydroxide to afford the corresponding 3-(4-aryl-3-cyano-2-methoxypyridin-6-yl)tropolones (**2a,c-i**) [**a**: R = H, 38%; **c**: R = 2-OCH_3, 43%; **d**: R = 3-OCH_3, 61%; **e**: R = 4-OCH_3, 51%; **f**: R = 2,4-$(OCH_3)_2$, 50%; **g**: R = 3,4-$(OCH_3)_2$, 55%; **h**: R = 2,3,4-$(OCH_3)_3$, 48%; **i**: R = 3,4-(OCH_2O), 76%]. In the reaction of 3-(4-chlorocinnamoyl)tropolone (**1j**) in the same conditions, the starting material was recovered. Using two molar equivalents of more strong base, sodium methoxide, the reaction at room temperature gave 3-[3-cyano-2-methoxy-4-(4-chlorophenyl)pyridin-6-yl]tropolone (**2j**) in 58% yield. The reaction of 3-(4-nitrocinnamoyl)tropolone (**1k**) in the presence of sodium methoxide also gave the corresponding 3-(6-pyridinyl)tropolone (**2k**) in 64% yield. The reaction of 3-(4-methylcinnamoyl)tropolone (**1b**) was carried out in ethanol in the presence of sodium hydroxide or ethoxide to afford 3-[3-cyano-3-ethoxy-4-(4-methylphenyl)pyridin-6-yl]tropolone (**3a**) in 44 and 41% yields, respectively. Similarly, compound (**1b**) reacted with malononitrile in 1-propanol in the presence of sodium 1-propoxide to give the corresponding product (**3b**) in 39% yield. The reactions might proceed *via* Michael addition of malononitrile to α,β-unsaturated carbonyl function in 3-cinnamoyltropolones (**1a-k**) followed by cyclization.

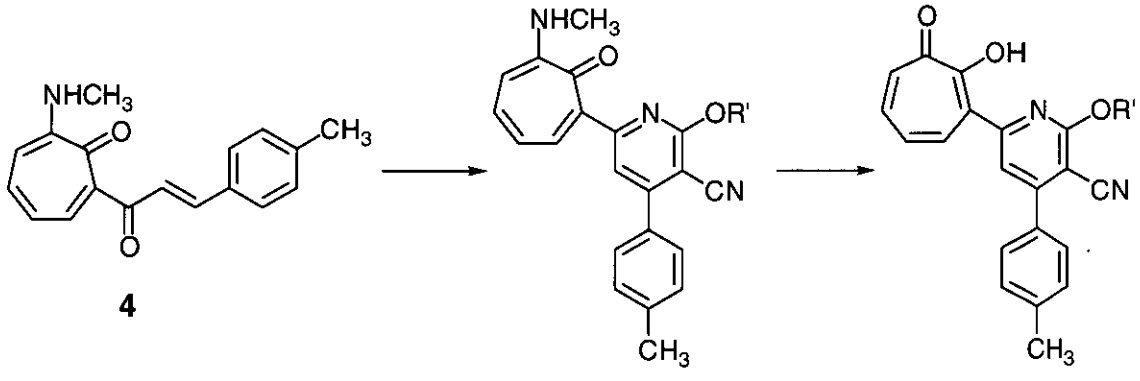


1 b **3 a, b**

Scheme 2

a R' = CH_2CH_3
b R' = $CH_2CH_2CH_3$

Reactions of 2-(4-Methylcinnamoyl)-7-methylaminotropone (4) with Malononitrile. 2-Cinnamoyl-7-methylaminotropones were readily obtained by the amination of 3-acetyltropolone followed by the reaction with benzaldehydes.[15] In order to examine the utility of them, the reactions of 2-(4-methylcinnamoyl)-7-methylaminotropone (**4**) were carried out. When a solution of 2-(4-methylcinnamoyl)-7-methylaminotropone (**4**) with malononitrile in methanol or ethanol was stirred for 24 h at room temperature in the presence of sodium methoxide or ethoxide, the corresponding 7-methylamino-2-(6-pyridinyl)tropones (**5a,b**) were obtained in 52 and 45% yields, respectively. Both the products (**5a,b**) were hydrolyzed to give 3-(6-pyridinyl)tropolones (**2b**) and (**3a**) in high yields.



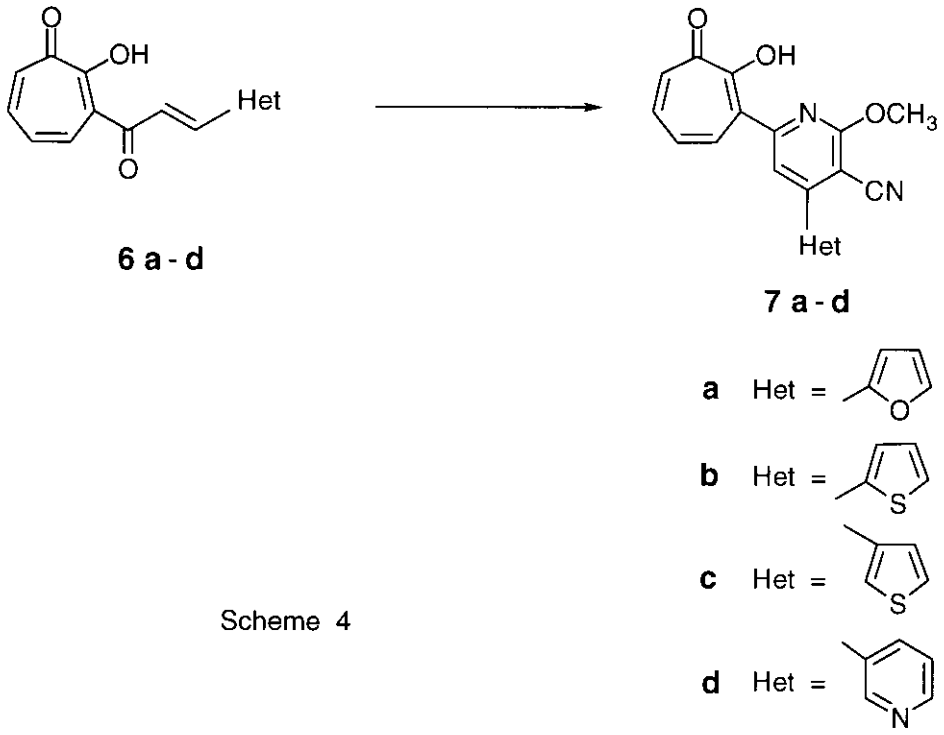
4 **5 a,b** **2 b, 3 a**

Scheme 3

a R' = CH_3
b R' = CH_2CH_3

2 b R' = CH_3
3 a R' = CH_2CH_3

Reactions of 3-(3-Heterocycle-substituted 2-Propenoyl)tropolones (6a-d) with Malononitrile. In a similar manner, analogous 3-(3-heterocycle-substituted 2-propenoyl)tropolones (**6a-d**) reacted with malononitrile at room temperature in the presence of sodium methoxide in methanol to give the corresponding 4'-heterocycle-substituted 3-(3-cyano-2-methoxypyridin-6-yl)tropolones (**7a-d**) in 60-65% yields.



Scheme 4

CONCLUSION

It was found that pyridine heterocycles having two different aromatic rings, tropolone and benzene or heterocyclic ring, were readily prepared at room temperature by the reactions of 3-cinnamoyltropolones and their heterocyclic analogues with malononitrile in the presence of two molar equivalents of base. The reactions of 3-cinnamoyltropolones (**1a-i**) having an electron-donating group such as methoxyl group proceeded smoothly at room temperature, while the reactions of tropolones (**1j,k**) having an electron-withdrawing group such as chlorine atom or nitro group needed more strong base, such as sodium methoxide. The reactions took place *via* Michael addition of malononirile into α,β-unsaturated carbonyl moiety of 3-cinnamoyltropolones followed by cyclization of the adducts. In the reactioins, an alkoxy group was captured from alcohols used as solvent.

EXPERIMENTAL

All the melting points were determined on a Yanagimoto MP S-2 apparatus and are uncorrected. The IR spectra were taken on a JASCO A-102 spectrophotometer. The NMR spectra were recorded with a JEOL JNM-EX 90 spectrometer (90 MHz for ^{1}H and 22.5 MHz for ^{13}C).

Materials. 3-Cinnamoyltropolones (**1a,c-e**),[13] (**1f-i**),[14] 2-(4-methylcinnamoyl)-7-methylaminotropone (**4**),[15] and heterocyclic analogues (**6a-d**)[16] were previously reported. Three 3-cinnamoyltropolones (**1b,j,k**) were newly prepared according to the literature method[13,14] from 3-acetyltropolone (2.0 mmol).

3-(4-Methylcinnamoyl)tropolone (1b). Pale yellow needles (from ethanol); yield 458 mg (86%); mp 184-185 °C; IR (KBr) ν 3179 (OH), 1645 (C=O), 1611 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, s, CH_3), 7.14 (1H, dd, J = 10.2, 9.6 Hz, H-6), 7.19 (1H, d, J = 16.1 Hz, H-2'), 7.19 (2H, d, J = 8.4 Hz, H-3",5"), 7.40 (1H, d, J = 10.2 Hz, H-7), 7.47 (2H, J = 8.4 Hz, H-2",6"), 7.49 (1H, dd, J = 10.4, 9.6 Hz, H-5), 7.61 (1H, d, J = 16.1 Hz, H-3'), 7.67 (1H, d, J = 10.4 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 121.3 (=C-), 124.6 (=C-), 127.8 (=C-), 128.7 (=C-), 129.6 (=C-), 131.7 (=C<), 137.2 =C<), 138.5 (=C-), 139.5 (=C-), 141.4 (=C<), 144.8 (=C-), 171.2 (=C<), 171.3 (=C<), 194.0 (C=O). *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 76.67; H, 5.30. Found: C, 77.00; H, 5.19.

3-(4-Chlorocinnamoyl)tropolone (1j). Yellow needles (from ethanol); yield 376 mg (75%); mp 190-191 °C; IR (KBr) ν 3180 (OH), 1645 (C=O), 1611 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.16 (1H, dd, J = 10.1, 9.6 Hz, H-6), 7.23 (1H, d, J = 16.1 Hz, H-2'), 7.36 (2H, d, J = 8.4 Hz, H-3",5"), 7.42 (1H, d, J = 101 Hz, H-7), 7.50 (1H, d, J = 16.1 Hz, H-3'), 7.52 (2H, d, J = 8.4 Hz, H-2",6"), 7.51 (1H, dd, J = 9.8, 9.6 Hz, H-5), 7.61 (1H, d, J = 16.1 Hz, H-3'), 7.73 (1H, d, J = 9.8 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 120.7 (=C-), 125.8 (=C-), 127.8 (=C-), 129.2 (=C-), 129.7 (=C-), 133.1 (=C<), 136. (=C<), 137.3 (=C<), 139.0 (=C-), 139.8 (=C-), 142.6 (=C-), 170.8 (=C<), 171.9 (=C<), 193.6 (C=O). *Anal.* Calcd for $C_{16}H_{11}O_3Cl$: C, 67.03; H, 3.78. Found: C, 67.33; H, 3.81.

3-(4-Nitrocinnamoyl)tropolone (1k). Yellow needles (from acetic acid); yield 404 mg (68%); mp 224-226 °C; IR (KBr) ν 3202 (OH), 1671 (C=O), 1614 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.19 (1H, dd, J = 10.1, 9.9 Hz, H-6), 7.41 (1H, d, J = 15.9 Hz, H-2'), 7.44 (1H, d, J = 10.1 Hz, H-7), 7.55 (1H, dd, J = 9.9, 9.6 Hz, H-5), 7.72 (1H, d, J = 15.9 Hz, H-3'), 7.74 (2H, d, J = 8.9 Hz, H-2",6"), 7.83 (1H, d, J = 9.6 Hz, H-4), 8.25 (2H, d, J = 8.9 Hz, H-3",5"). *Anal.* Calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.63; H, 3.69; N, 4.82.

Reactions of 3-Cinnamoyltropolones (1a-k) with Malononitrile. a) To a solution of 3-cinnamoyltropolone (**1a-i**) (1.0 mmol) and malononitrile (122 mg, 2.0 mmol) in methanol (10 mL) was added sodium hydroxide (80 mg, 2.0 mmol). After stirring for 24 h at rt, the mixture was neutralized with acetic acid to yield 3-(4-aryl-3-cyano-2-methoxypyridin-6-yl)tropolones (**2a-i**) as precipitate. Each product was recrystallized from ethanol.

3-(3-Cyano-2-methoxy-4-phenylpyridin-6-yl)tropolone (2a). Yellow crystals (from ethanol); yield 126 mg (38%); mp 236-237 °C; IR (KBr) ν 3118 (OH), 2215 (C≡N), 1600 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$+CF_3COOD) δ 4.32 (3H, s, OCH_3), 7.62-7.98 (9H, m), 7.89 (1H, s, H-5'), 8.44 (1H, d, J =

10.0 Hz, H-4). *Anal.* Calcd for $C_{20}H_{14}N_2O_3$: C, 72.70; H, 4.27; N, 8.48. Found: C, 72.68; H, 4.24; N, 8.28.

3-[3-Cyano-2-methoxy-4-(4-methylphenyl)pyridin-6-yl]tropolone (2b). Yellow crystals (from ethanol); yield 183 mg (53%); mp 243-244 °C; IR (KBr) ν 3116 (OH), 2214 (C≡N), 1600 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 2.44 (3H, s, CH_3), 4.26 (3H, s, OCH_3), 7.34 (2H, d, J = 8.2 Hz, H-3",5"), 7.58 (2H, d, J = 8.2 Hz, H-2",6"), 7.65-7.90 (4H, m), 7.77 (1H, s, H-5'), 8.37 (1H, d, J = 10.0 Hz, H-4). *Anal.* Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.32; H, 4.64; N, 8.03.

3-[3-Cyano-2-methoxy-4-(2-methoxylphenyl)pyridin-6-yl]tropolone (2c). Yellow crystals (from ethanol); yield 155 mg (43%); mp 204-206 °C; IR (KBr) ν 3116 (OH), 2215 (C≡N), 1596 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 3.83 (3H, s, OCH_3-2"), 4.10 (3H, s, OCH_3-2'), 7.18-7.53 (8H, m), 7.76 (1H, s, H-5'), 8.21 (1H, d, J = 10.0 Hz, H-4); ^{13}C NMR (DMSO-d_6) δ 36.7 (OCH_3), 37.6 (OCH_3), 94.9 (=C<), 111.9 (=C-), 114.8 (=C<), 119.7 (=C-), 120.1 (=C-), 120.7 (=C-), 124.7 (=C<), 126.8 (=C-), 130.0 (=C-), 131.4 (=C-), 135.8 (=C<), 138.4 (=C-), 140.3 (=C-), 153.0 (=C<), 155.9) =C<), 157.5 (=C<), 163.7 (=C<), 169.6 (=C<), 172.8 (=C<). *Anal.* Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.78. Found: C, 69.82; H, 4.48; N, 7.76.

3-[3-Cyano-2-methoxy-4-(3-methoxylphenyl)pyridin-6-yl]tropolone (2d). Yellow crystals (from ethanol); yield 220 mg (61%); mp 253-255 °C; IR (KBr) ν 3200 (OH), 2218 (C≡N), 1601 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 3.94 (3H, s, OCH_3-3"), 4.37 (3H, s, OCH_3-2'), 7.17-8.06 (7H, m), 7.24 (1H, s, H-2"), 7.90 (1H, s, H-5'), 8.56 (1H, d, J = 10.0 Hz, H-4). *Anal.* Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.78. Found: C, 69.59; H, 4.46; N, 7.71.

3-[3-Cyano-2-methoxy-4-(4-methoxylphenyl)pyridin-6-yl]tropolone (2e). Yellow crystals (from ethanol); yield 180 mg (50%); mp 282-284 °C; IR (KBr) ν 3205 (OH), 2220 (C≡N), 1600 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 3.92 (3H, s, OCH_3-4"), 4.29 (3H, s, OCH_3-2'), 7.09 (2H, d, J = 8.8 Hz, H-3",5"), 7.55-7.92 (4H, m), 7.68 (2H, d, J = 8.8 Hz, H-2",6"), 7.79 (1H, s, H-5'), 8.41 (1H, d, J = 9.9 Hz, H-4). *Anal.* Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.78. Found: C, 69.92; H, 4.39; N, 7.48.

3-[3-Cyano-2-methoxy-4-(2,4-dimethoxylphenyl)pyridin-6-yl]tropolone (2f). Yellow crystals (from ethanol); yield 195 mg (50%); mp 192-194 °C; IR (KBr) ν 3318 (OH), 2204 (C≡N), 1611 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.85 (3H, s, OCH_3-2"+OCH_3-4"), 4.12 (3H, s, OCH_3-2'), 6.56-6.66 (2H, m), 7.06-7.60 (4H, m), 7.40 (1H, s, H-3"), 7.83 (1H, s, H-5'), 8.25 (1H, d, J = 10.0 Hz, H-4). *Anal.* Calcd for $C_{22}H_{18}N_2O_5$: C, 67.68; H, 4.65; N, 7.18. Found: C, 67.40; H, 4.53; N, 7.18.

3-[3-Cyano-2-methoxy-4-(3,4-dimethoxylphenyl)pyridin-6-yl]tropolone (2g). Yellow crystals (from ethanol); yield 215 mg (55%); mp 232-234 °C; IR (KBr) ν 3185 (OH), 2203 (C≡N), 1600 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 3.99 (3H, s, OCH_3-3" or OCH_3-4"), 4.01 (3H, s, OCH_3-3" or OCH_3-4"), 4.47 (3H, s, OCH_3-2'), 7.14 (1H, d, J = 8.9 Hz, H-5"), 7.34 (1H, s, H-2"), 7.32-7.91 (4H, m), 8.01 (1H, s, H-5'), 8.08 (1H, d, J = 8.9 Hz, H-6"), 8.69 (1H, d, J = 10.0 Hz, H-4). *Anal.* Calcd for $C_{22}H_{18}N_2O_5$: C, 67.68; H, 4.65; N, 7.18. Found: C, 67.72; H, 4.67; N, 7.27.

3-[3-Cyano-2-methoxy-4-(2,3,4-trimethoxylphenyl)pyridin-6-yl]tropolone (2h). Yellow crystals (from ethanol); yield 202 mg (48%); mp 194-195 °C; IR (KBr) ν 3365 (OH), 2224 (C≡N), 1598 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.87 (3H, s, OCH_3), 3.91 (6H, s, 2×OCH_3), 4.14 (3H, s, OCH_3-2'), 6.76 (1H, d, J = 8.6 Hz, H-5''), 7.12 (1H, d, J = 8.6 Hz, H-6''), 7.31-7.49 (4H, m), 7.87 (1H, s, H-5'), 8.28 (1H, d, J = 9.6 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 54.5 (OCH_3), 56.1 (OCH_3), 61.0 (OCH_3), 61.5 (OCH_3), 107.3 (=C-), 115.3 (=C<), 120.6 (=C-), 120.9 (=C-), 122.8 (=C<), 124.9 (=C-), 127.3 (=C-), 135.1 (=C<), 138.6 (=C-), 141.2 (=C-), 142.3 (=C<), 151.3 (=C<), 153.5 (=C<), 155.9 (=C<), 164.3 (=C<), 166.6 (=C<), 170.7 (=C<), 171.8 (=C<). *Anal.* Calcd for $C_{23}H_{20}N_2O_6$: C, 65.70; H, 4.80; N, 6.66. Found: C, 65.44; H, 4.79; N, 6.72.

3-[3-Cyano-2-methoxy-4-(3,4-methylenedioxylphenyl)pyridin-6-yl]tropolone (2i). Yellow crystals (from ethanol); yield 284 mg (76%); mp >300 °C; IR (KBr) ν 3179 (OH), 2216 (C≡N), 1602 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 4.44 (3H, s, OCH_3), 6.12 (2H, s, OCH_2O), 6.98 (1H, s, H-2''), 7.12 (1H, d, J = 9.6 Hz, H-5''), 7.77 (1H, d, J = 9.6 Hz, H-6''), 7.93 (1H, s, H-5'), 7.98-8.11 (4H, m), 8.65 (1H, d, J = 9.8 Hz, H-4). *Anal.* Calcd for $C_{21}H_{14}N_2O_5$: C, 67.37; H, 3.77; N, 7.49. Found: C, 67.12; H, 3.78; N, 7.51.

b) 3-Cinnamoyltropolone (**1j-k**) (1.0 mmol) and malononitrile (122 mg, 2.0 mmol) was added to sodium methoxide solution, prepared from sodium (46 mg, 2.0 mmol) and methanol (10 mL). The solution was stirred for 24 h at rt and worked up, as described above, to yield 3-(4-aryl-3-cyano-2-methoxypyridin-6-yl)tropolones (**2j-k**).

3-[4-(4-Chlorophenyl)-3-cyano-2-methoxypyridin-6-yl]tropolone (2j). Yellow crystals (from ethanol); yield 212 mg (58%); mp 274-276 °C; IR (KBr) ν 3188 (OH), 2214 (C≡N), 1598 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 4.37 (3H, s, OCH_3), 7.65 (2H, d, J = 8.9 Hz, H-2'',6''), 7.82-8.09 (6H, m), 7.88 (1H, s, H-5'), 8.58 (1H, d, J = 10.4 Hz, H-4). *Anal.* Calcd for $C_{20}H_{13}N_2O_3Cl$: C, 65.85; H, 3.59; N, 7.68. Found: C, 65.84; H, 3.65; N, 7.70.

3-[3-Cyano-2-methoxy-4-(4-nitrophenyl)pyridin-6-yl]tropolone (2k). Yellow crystals (from ethanol); yield 240 mg (64%); mp 263-265 °C; IR (KBr) ν 3118 (OH), 2204 (C≡N), 1602 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 4.20 (3H, s, OCH_3), 7.48-7.84 (6H, m), 7.87 (1H, s, H-5'), 8.24 (1H, d, J = 10.1 Hz, H-4), 8.58 (2H, d, J = 8.9 Hz, H-3'',5''). *Anal.* Calcd for $C_{20}H_{13}N_3O_5$: C, 64.00; H, 3.49; N, 11.20. Found: C, 64.36; H, 3.53; N, 11.09.

c) A solution of 3-(4-methylcinnamoyl)tropolone (**1b**) (266 mg, 1.0 mmol) and malononitrile (122 mg, 2.0 mmol) in sodium ethoxide solution, prepared from sodium (46 mg, 2.0 mmol) and ethanol (10 mL), was stirred for 24 h at rt and worked up, as described above, to afford 3-[3-cyano-2-ethoxy-4-(4-methylphenyl)pyridin-6-yl]tropolone (**3a**), yellow crystals (from ethanol); yield 147 mg (41%); mp 193-195 °C; IR (KBr) ν 3117 (OH), 2216 (C≡N), 1601 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.48 (3H, t, J = 7.0 Hz, CH_2CH_3), 2.41 (3H, s, CH_3-4''), 4.58 (2H, q, J = 7.0 Hz, CH_2), 7.18-7.48 (6H, m), 7.58 (2H, d, J = 8.4 Hz, H-2'',6''), 7.87 (1H, s, H-5'), 8.21 (1H, d, J = 9.6 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_2CH_3), 21.2 (CH_3-4'), 63.4 (CH_2), 119.2 (=C-), 120.4 (=C-), 127.3 (=C-), 128.4 (=C-), 129.5 (=C-), 133.2 (=C<), 135.2 (=C<), 138.6 (=C-), 140.2 (=C<), 141.1 (=C-), 155.9 (=C<), 156.4 (=C<),

164.5 (=C<), 170.5 (=C<), 171.9 (=C<). *Anal.* Calcd for $C_{22}H_{18}N_2O_3$: C, 73.78; H, 5.06; N, 7.82. Found: C, 74.07; H, 5.23; N, 7.82.

d) A solution of 3-(4-methylcinnamoyl)tropolone (**1b**) (266 mg, 1.0 mmol) and malononitrile (122 mg, 2.0 mmol) in sodium 1-propoxide solution, prepared from sodium (46 mg, 2.0 mmol) and 1-propanol (10 mL), was stirred for 24 h at rt and worked up, as described above, to afford 3-[3-cyano-4-(4-methylphenyl)-2-(1-propoxy)pyridin-6-yl]tropolone (**3b**), yellow crystals (from ethanol); yield 142 mg (38%); mp 179-181 °C; IR (KBr) ν 3123 (OH), 2214 (C≡N), 1596 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.38 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.81 (2H, m, CH_2), 2.40 (3H, s, CH_3-4"), 4.47 (2H, q, J = 6.4 Hz, OCH_2), 7.18-7.47 (6H, m), 7.57 (2H, d, J = 8.4 Hz, H-2",6"), 7.87 (1H, s, H-5'), 8.22 (1H, d, J = 9.8 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 10.4 (CH_2CH_3), 21.2 (CH_2CH_3), 22.1 (CH_3-4'), 69.0 (OCH_2), 115.2 (=C-), 119.1 (=C-), 120.3 (=C-), 127.2 (=C-), 128.3 (=C-), 129.5 (=C-), 133.1 (=C-), 135.2 (=C<), 138.5 (=C-), 140.1 (=C-), 141.0 (=C-), 155.8 (=C<), 156.4 (=C<), 164.5 (=C<), 170.4 (=C<), 171.9 (=C<). *Anal.* Calcd for $C_{23}H_{20}N_2O_3$: C, 74.17; H, 5.41; N, 7.52. Found: C, 74.37; H, 5.44; N, 7.54.

Reactions of 3-(4-Methylcinnamoyl)-7-methylaminotropone (4) with Malononitrile. a) A mixture of 3-(4-methylcinnamoyl)-7-methylaminotropone (**4**) (265 mg, 1.0 mmol) and maolononitrile (122 mg, 2.0 mmol) in sodium methoxide solution, prepared from sodium (46 mg, 2.0 mmol) and absolute methanol (20 mL), was stirred for 24 h at rt, and worked up, as described above, to yield 2-(3-cyano-2- methoxy-4-phenylpyridin-6-yl)-7-methylaminotropone (**5a**), yellow crystals (from ethanol); yield 179 mg (52%); mp 245-247 °C; IR (KBr) ν 3255 (NH), 2214 (C≡N), 1602 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 3.10 (3H, d, J = 5.4 Hz, NCH_3), 4.13 (3H, s, OCH_3), 6.58 (1H, d, J = 10.3 Hz), 6.87 (1H, d, J = 9.9 Hz), 7.38-7.69 (6H, m), 7.86 (1H, s, H-5'), 8.11 (1H, d, J = 9.8 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 29.9 (NCH_3), 54.5 (OCH_3), 108.5 (=C-), 113.9 (=C<), 115.9 (=C<), 119.6 (=C-), 121.0 (=C-), 128.6 (=C-), 128.7 (=C-), 129.6 (=C-), 134.7 (=C<), 136.5 (=C<), 138.0 (=C-), 140.0 (=C-), 155.2 (=C<), 158.4(=C<), 158.6 (=C<), 159.7 (=C<), 173.7 (=C<). *Anal.* Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.52; H, 4.99; N, 12.09.

b) The reaction of **4** (265 mg, 1.0 mmol) with malononitrile (122 mg, 2.0 mmol) in sodium ethoxide, prepared from sodium (46 mg, 2.0 mmol) and absolute ethanol (10 mL), was carried out and worked up, as described above, to give 2-(3-cyano-2-ethoxy-4-phenylpyridin-6-yl)-7-methylaminotropone (**6b**), yellow crystals (from ethanol); yield 161 mg (45%); mp 185-186 °C; IR (KBr) ν 3256 (NH), 2216 (C≡N), 1600 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.48 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.08 (3H, d, J = 4.4 Hz, NCH_3), 4.59 (2H, q, J = 7.0 Hz, OCH_2), 6.56 (1H, d, J = 10.1 Hz), 6.74 (1H, d, J = 9.8 Hz), 7.36-7.72 (6H, m), 7.82 (1H, s, H-5'), 8.08 (1H, d, J = 9.8 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_2CH_3), 29.8 (NCH_3), 63.2 (OCH_2), 92.6 (=C<), 108.5 (=C-), 115.8 (=C<), 119.3 (=C-), 120.9 (=C-), 128.5 (=C-), 128.7 (=C-), 129.6 (=C-), 134.8 (=C-), 136.6 (=C<), 137.9 (=C-), 139.9 (=C-), 155.2 (=C<), 158.6 (=C<), 159.8 (=C<), 164.5 (=C<), 173.7 (=C<). *Anal.* Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.71; H, 5.31; N, 11.64.

c) A suspended solution of 2-(2-alkoxy-3-cyano-4-phenylpyridin-6-yl)-7-methylaminotropone (**5a,b**) (0.5 mmol) in water (4 mL) was refluxed for 18 h (for **5a**) or 20 h (for **5b**) in the presence of sodium hydroxide

(40 mg, 1.0 mmol). The mixture was neutralized with acetic acid to precipitate 3-(2-alkoxy-3-cyano-4-phenylpyridin-6-yl)tropolones (**2b**,**3a**).

3-(3-Cyano-2-methoxy-4-phenylpyridin-6-yl)tropolone (2b). Yield 153 mg (92%).

3-(3-Cyano-2-ethoxy-4-phenylpyridin-6-yl)tropolone (3a). Yellow crystals (from ethanol); yield 300 mg (87%); mp 231-232 °C; IR (KBr) ν 3148 (OH), 2224 (C≡N), 1612 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 1.67 (3H, t, J = 7.0 Hz, CH_2CH_3), 4.78 (2H, q, J = 7.0 Hz, CH_2), 7.64-8.06 (9H, m), 7.93 (1H, s, H-5'), 8.61 (1H, d, J = 10.6 Hz, H-4). *Anal.* Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.39; H, 4.67; N, 8.04.

Reactions of 3-(3-Heterocycle-substituted 2-Propenoyl)tropolones (6a-d) with Malononitrile. A solution of 3-(3-heterocycle-substituted 2-propenoyl)troplone **7a-d** (1.0 mmol) and malononitrile (122 mg, 2.0 mmol) in methanol (10 mL) was stirred for 24 h at rt in the presence of sodium hydroxide (80 mg, 2.0 mmol). The mixture was neutralized with acetic acid and worked up, as described above, to give 3-(4-heterocycle-substituted 3-cyano-2-methoxypyridin-6-yl)tropolones (**7a-d**).

***3-[3-Cyano-2-methoxy-4-(2-furyl)pyridin-6-yl]tropolone* (7a).** Yellow crystals (from ethanol); yield 208 mg (65%); mp 237-239 °C; IR (KBr) ν 3259 (OH), 2211 (C≡N), 1602 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 4.45 (3H, s, OCH_3), 6.78-6.84 (1H, m), 7.72-8.12 (6H, m), 8.28 (1H, s), 8.68 (1H, d, J = 10.3 Hz). *Anal.* Calcd for $C_{18}H_{12}N_2O_4$: C, 67.49; H, 3.78; N, 8.75. Found: C, 67.29; H, 3.66; N, 8.42.

3-[3-Cyano-2-methoxy-4-(2-thienyl)pyridin-6-yl]tropolone (7b). Yellow crystals (from ethanol); yield 202 mg (60%); mp 232-233 °C; IR (KBr) ν 3214 (OH), 2216 (C≡N), 1598 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 4.23 (3H, s, OCH_3), 7.27-7.31 (1H, m), 7.51-8.04 (6H, m), 7.88 (1H, s), 8.29 (1H, d, J = 9.9 Hz). *Anal.* Calcd for $C_{18}H_{12}N_2O_3S$: C, 64.27; H, 3.60; N, 8.33. Found: C, 64.06; H, 3.63; N, 7.97.

3-[3-Cyano-2-methoxy-4-(3-thienyl)pyridin-6-yl]tropolone (7c). Yellow crystals (from ethanol); yield 205 mg (61%); mp 256-258 °C; IR (KBr) ν 3143 (OH), 2206 (C≡N), 1600 cm^{-1} (C=O); ^1H NMR (DMSO-d_6) δ 4.08 (3H, s, OCH_3), 7.22-7.85 (7H, m), 7.92 (1H, s), 8.14 (1H, d, J = 9.2 Hz). *Anal.* Calcd for $C_{18}H_{12}N_2O_3S$: C, 64.27; H, 3.60; N, 8.33. Found: C, 63.92; H, 3.50; N, 8.16.

3-[3-Cyano-2-methoxy-4-(3-pyridyl)pyridin-6-yl]tropolone (7d). Yellow crystals (from ethanol); yield 205 mg (62%); mp >300 °C; IR (KBr) ν 3255 (OH), 2214 (C≡N), 1602 cm^{-1} (C=O); ^1H NMR ($CDCl_3$+CF_3COOD) δ 4.22 (3H, s, OCH_3), 7.47-7.74 (4H, m), 7.82 (1H, s), 8.20-8.33 (2H, m), 8.83-9.12 (2H, m), 9.25 (1H, s). *Anal.* Calcd for $C_{19}H_{13}N_3O_3$: C, 68.88; H, 3.95; N, 12.68. Found: C, 68.89; H, 3.86; N, 12.57.

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