# Cycloaddition of 3-Amino-5-chloro-2(1*H*)-pyrazinones and Olefins: Ring Transformation into 3-Amino- or 6-Cyano-Substituted 2-Pyridinone Systems

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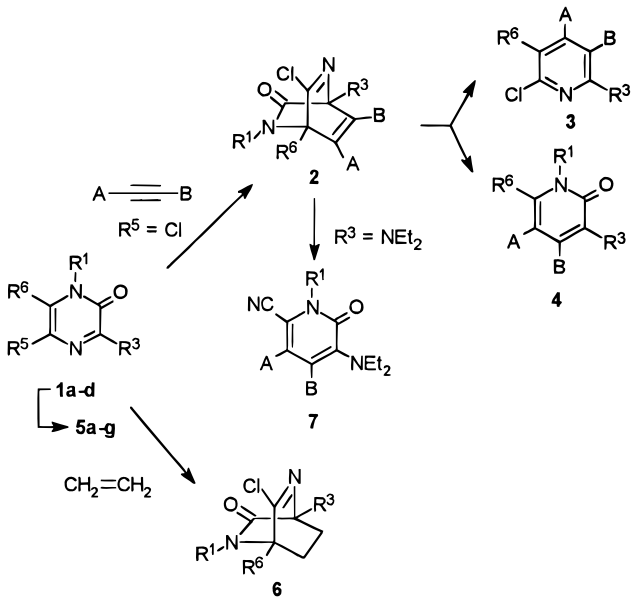
The cycloadducts formed from the Diels−Alder reaction of 3-amino-5-chloro-2(1*H*)-pyrazinones with methyl acrylate in toluene are subject to two alternative modes of ring transformation yielding either methyl 6-cyano-1,2-dihydro-2-oxo-4-pyridinecarboxylates, e.g. **12a,b** (loss of amine substituent), or the corresponding 3-amino-6-cyano-1,2,5,6-tetrahydro-2-oxo-4-pyridinecarboxylates, e.g. **15a,b**. From the latter compounds, 3-amino-2-pyridinones can be generated through subsequent loss of HCN. A mechanism accounting for the loss or retention of the amine substituent is based on (1) the effects observed for each reaction mode when varying the substituents in both reaction partners and (2) the exclusive retention of the amine substituent when replacing toluene with the basic solvent pyridine.

Several heterocycles containing a 2-aza diene system are subject to undergo cycloaddition and subsequent elimination reactions.[1] In previous work of our group the 3,5-dichloro-2(1*H*)-pyrazinones of type **1a**−**d**, easily prepared from α-amino nitriles and oxalyl chloride,[2] and some 3-substituted derivatives were shown to react with acetylenic compounds in two divergent ways.[3] Depending on the substitution pattern of both the 2(1*H*)-pyrazinone and the dienophile, the initially formed cycloadducts **2** gave pyridines **3** and/or 2(1*H*)-pyridinones **4** (Scheme 1). Cycloaddition of compounds **1a**−**d** with olefins afforded stable bicyclic products **6**.[4,5] The intermediate adducts **2** ($R^3$ = $NEt_2$) formed from 3-amino-5-chloro-2(1*H*)-pyrazinones of type **5a,b** and acetylenic compounds, in contrast to the reaction of other 3-substituted 2(1*H*)-pyrazinones ($R^3 \neq NR_2$), where found[6] to undergo ring transformations resulting in production of compounds **7**. Although ring transformation reactions are common in heterocyclic chemistry,[7] to our knowledge a rearrangement of the type proposed has not been described. An analogous amino-substituted aza diene system has been dealt with only in a few papers,[8] and only in a single case could the product obtained after Diels−Alder reaction be interpreted by a similar mechanism.[9] We now report on two alternative modes of ring transformation observed

**Scheme 1**




| | $R^1$ | $R^3$ | $R^5$ | $R^6$ |
|---|---|---|---|---|
| **1a** | Ph | Cl | Cl | H |
| **1b** | Me | Cl | Cl | H |
| **1c** | Ph | Cl | Cl | Me |
| **1d** | Bn | Cl | Cl | H |
| **5a** | Ph | $NEt_2$ | Cl | H |
| **5b** | Me | $NEt_2$ | Cl | H |
| **5c** | Ph | $NEt_2$ | Cl | Me |
| **5d** | Ph | $NEt_2$ | H | H |
| **5e** | Me | NHEt | Cl | H |
| **5f** | Me | $NH_2$ | Cl | H |
| **5g** | Bn | 3-indolyl | Cl | H |

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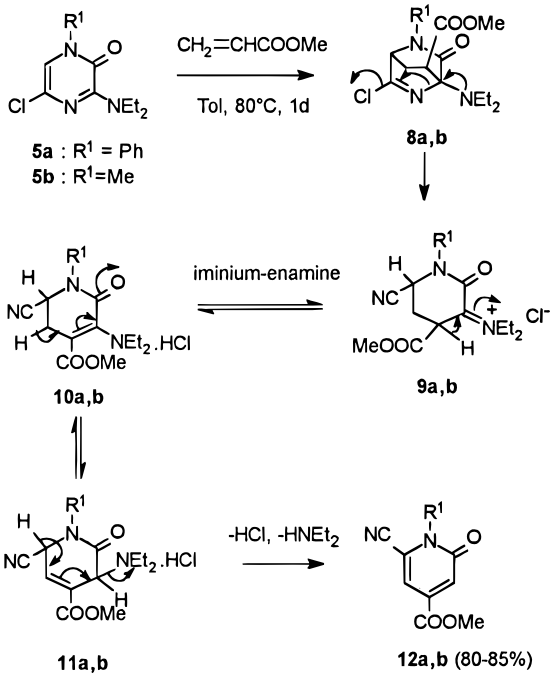
0022-3263/96/1961-0304$12.00/0 

**Scheme 2**

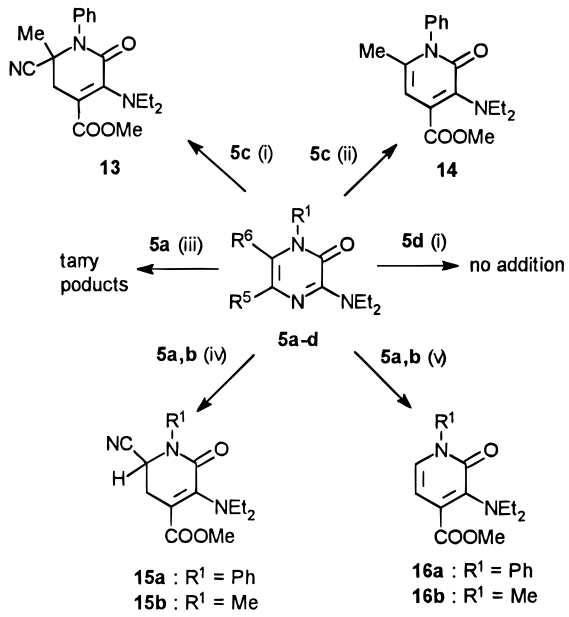



in cycloadducts of 3-amino-5-chloro-2(1*H*)-pyrazinones **5a**−**g** and some *olefinic* dienophiles.

As a model for our investigations we used the reaction between methyl acrylate and 5-chloro-3-(diethylamino)-2(1*H*)-pyrazinones (**5a,b**). Upon reaction with 3 equiv of methyl acrylate in toluene at 80 °C for about 20 h, instead of the normally expected adducts of type **8a,b**, we isolated methyl 6-cyano-1,2-dihydro-2-oxo-4-pyridinecarboxylate (**12a,b**) as the sole reaction product (Scheme 2). The $^1$H NMR spectra of these compounds show a characteristic $^4J$ coupling of 2 Hz for the protons in the 3 and 5 position. The IR absorptions at about 2225 (nitrile) and 1735 cm$^{-1}$ (ester) are in agreement with the structure proposed. Compounds **12a,b** may originate from a rearrangement similar to that already described for the acetylene type cycloadducts.[6] In the original olefin type cycloadducts, the 2,5-diazabicyclo[2.2.2]oct-2-ene compounds **8a,b**, cleavage of the ring C−N bond again may be assisted by the nitrogen electron pair to form intermediates **9a,b**. They can be transformed into tautomeric forms **10a,b** and **11a,b** *via* successive acid-catalyzed equilibration, resulting in the final loss of the protonated diethylamino group and formation of compounds **12a,b**.

The chlorine atom in the 5 position and the hydrogen substituent in the 6 position of the 2(1*H*)-pyrazinones (**5**) are crucial factors for the proposed reaction route, because they are serving as a leaving group and an acidic proton, respectively. In order to confirm the role of the 5-chlorine substituent, which was essential in the reaction with acetylenic compounds, we tried the addition of methyl acrylate on the dechlorinated analogue **5d**. However, cycloaddition of **5d** proved unsuccessful, as found already with other 5-dechlorinated 2(1*H*)-pyrazinones.[5] To investigate the role of the 6-H atom, the 6-methyl-substituted pyrazinone **5c** was made to react with methyl acrylate in toluene at 80 °C for 1 d. After workup and column chromatography on silica gel, two new products were isolated, i.e. the 6-cyano compound **13** (41%) and the corresponding elimination product **14** (13%). In the $^1$H NMR spectrum of **13**, the 5-methylene protons appeared as two doublets at 3.15 and 2.95 ppm with a $J_{gem}$ of 17 Hz. Compound **14** was identical to the product isolated previously in low yield from the reaction of **5c** with methyl propynoate.[6] Complete conversion of the intermediate compound **13** to the final product **14** was observed when the cycloaddition of **5c** with methyl acrylate was conducted under forcing conditions (toluene, reflux for 2 d, 83%). Heating of the isolated compound **13** (toluene, reflux for 2 d) also led to a quantitative conversion. The isolation of **13**, the free base analogue of the salt intermediates **10a,b** provides support for the mechanism depicted in Scheme 2. Due to the absence of a hydrogen atom in the 6 position, the loss of diethylamine hydrochloride is prevented; elimination of hydrogen cyanide can occur under more forcing conditions.

**Scheme 3**

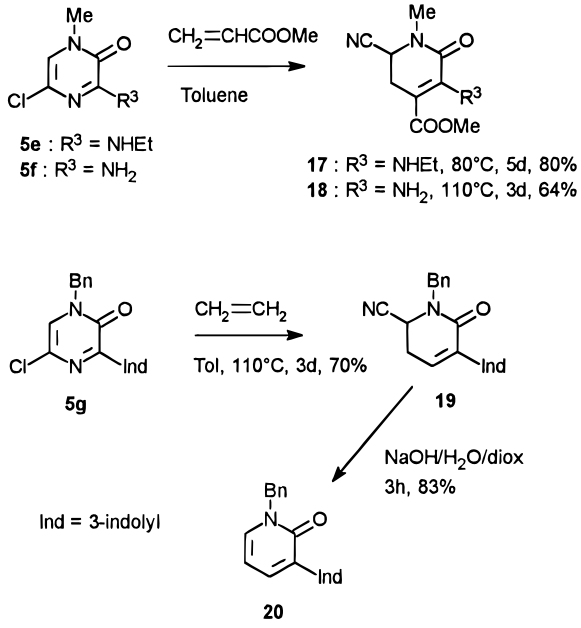



(i) 3 eq $CH_2$=CHCOOMe, Tol, 80°C, 1d
(ii) 3 eq $CH_2$=CHCOOMe, Tol, reflux, 2d, 83%
(iii) 3 eq $CH_2$=C(Me)COOMe, Tol, 80°c, 2d
(iv) 3 eq $CH_2$=CHCOOMe, Pyr, 80°C, 10h
(v) 3 eq $CH_2$=CHCOOMe, Pyr, reflux, 2d, 70-75%

To clarify the role of the acidic proton in the α position of the ester group in intermediates **9a,b**, compound **5a** was made to react with methyl methacrylate in toluene at 80 °C. Not unexpectedly a mixture of tarry products was formed.

Since the ring transformation depicted in Scheme 2 involves successive acid-catalyzed tautomerizations resulting in expulsion of diethylamine hydrochloride, a marked influence on the outcome of the cycloaddition of **5a,b** was to be expected when using a basic solvent, i.e. dry pyridine. This modification indeed resulted (Scheme 3) in isolation of the unstable 3-amino intermediates **15a,b** when the reaction was conducted at 80 °C for 10 h. When more drastic conditions were applied, i.e. reflux temperature for 2 d, products **16a,b** corresponding to further elimination of HCN were isolated in good yield. On the other hand, ring transformation of the ester enamine intermediate **15a**, to form **12a** according to the reaction sequence depicted in Scheme 2, could be effected in two different ways. Treatment of **15a** with dry HCl in toluene and further heating of the precipitated salt (**10a**)−solvent mixture at 80 °C quickly afforded the

**Scheme 4**



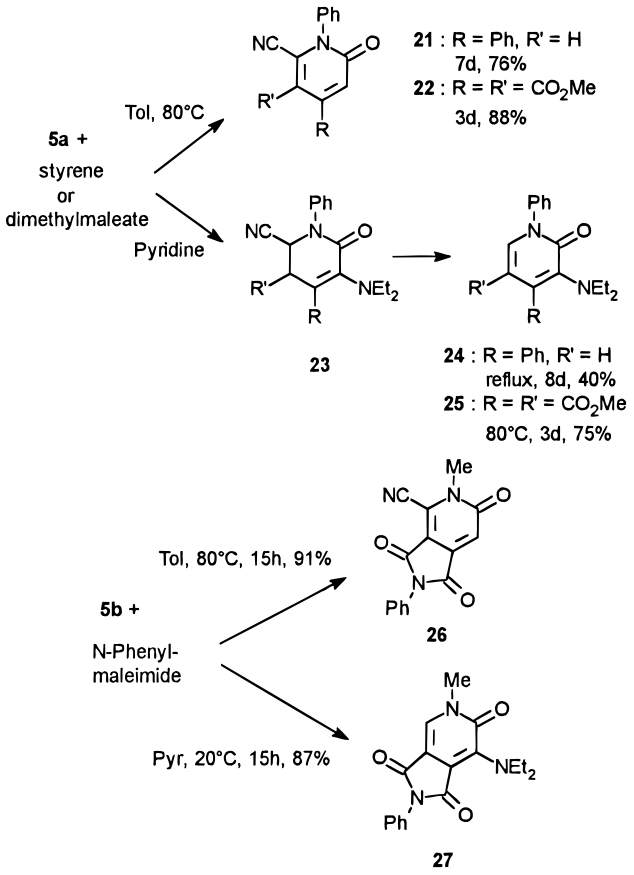

expected product **12a**. For the analogous conversion of the free base **15a**, prolonged reflux in toluene was required. These observations strongly support the intermediacy of the protonated ester enamine **9a,b** and its tautomeric forms **10a,b** and **11a,b**. Apparently, deprotonation of these intermediates is effected with pyridine, which retards the elimination of diethylamine (**15a,b** → **12a,b**) and favors the loss of HCN (**15a,b** → **16a,b**).

The nature of the amine substituent in the 3 position of the starting 2(1*H*)-pyrazinone (**5**) also appears to be important. Cycloaddition of 3-(ethylamino)- and 3-amino-2(1*H*)-pyrazinones (**5e,f**) (Scheme 4) with methyl acrylate in toluene proceeded slowly (5 d at 80 °C, 3 d at 110 °C, respectively), affording the rearranged compounds **17** and **18** which did not lose hydrogen cyanide under these conditions. Retention of the amine substituent also was observed in the reaction of ethene with the 3-indolyl-2(1*H*)-pyrazinone (**5g**), wherein the indolyl group can be considered as a vinylogous amine. The unstable reaction product **19** was characterized after HPLC purification (10% ethyl acetate/chloroform). Treatment of a dioxane solution of compound **19** with aqueous sodium hydroxide led to complete conversion into the pyridinone elimination product **20**.

To probe the general scope of the rearrangement, we investigated the reaction of **5a** with other olefins, i.e. styrene and dimethyl maleate, under standard conditions (toluene, 80 °C, 7 and 3 d, respectively). The expected cyano-substituted 6-oxopyridine derivatives **21** and **22** were isolated (Scheme 5). For the reaction of **5a** with styrene in pyridine, reflux conditions were required; after 2 d this resulted in a mixture of the 2-pyridinecarbonitrile derivative **23** (R = Ph, R′ = H) and the 3-(diethylamino)-2(1*H*)-pyridinone (**24**). Further reflux for 6 d led to complete conversion of **23** into **24**. The analogous reaction with dimethyl maleate in pyridine (80 °C, 3 d) afforded **25** (75%).

*N*-Phenylmaleimide, a powerful cyclic dienophile, reacted with **5b** in toluene at room temperature to give the pyrrolopyridine **26**. Reaction in dry pyridine afforded the expected diethylamino derivative **27**. Compounds of type

**Scheme 5**




**26** and **27** have been described scarcely and are not easily accessible.[10]

We may therefore conclude that ring transformations of the cycloadducts from olefins with 3-amino-2(1*H*)-pyrazinones proceed with or without loss of the amine substituent. Expulsion of the amine to produce 6-cyano-2(1*H*)-pyridinone systems can occur only if four structural conditions are fulfilled. For the pyrazinone these are as follows: (1) a leaving group at position 5, (2) a hydrogen atom at position 6, and (3) a diethylamino group at position 3. For the alkene component at least one hydrogen on each of the original double bond positions is required to allow for generation of the tautomeric intermediates **9** and **10**. The amine substituent is retained in the alternative mode of ring transformation. This occurs when 6-H is replaced with a methyl group or when an ethylamino or indolyl group is present at the 3 position. Moreover, deprotonation of the iminium ester intermediate **9**, when using pyridine as a solvent instead of toluene, induces a complete change from the first to the second mode of ring transformation. This produces compounds of type **13**, **15**, **17**−**19**, and **23** which in some cases may lose HCN to form compounds of type **14**, **16**, **20**, **24**, **25**, or **27**.

## Experimental Section

For general instrument conditions, see ref 6. All crystallizations were carried out in hexane/$CHCl_3$ unless stated otherwise. The 3,5-dichloro-2(1*H*)-pyrazinones (**1a,b,d**)[1] and the 3-(diethylamino)- and 3-amino-2(1*H*)-pyrazinones (**5a,b**, and **5f**)[6] were reported previously.

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**3,5-Dichloro-6-methyl-1-phenyl-2(1*H*)-pyrazinone (1c).** Compound **1c** was prepared as reported previously:[1] yield 48%; mp 182−183 °C; IR (KBr) 1670, 1600 $cm^{-1}$; $^1H$ NMR $\delta$ 2.08 (s, 3 H), 7.15−7.60 (m, 5 H); MS *m*/*z* 254 ($M^+$), 226, 77; exact mass calcd for $C_{11}H_8Cl_2N_2O$ 254.0014, found 254.0032.

**5-Chloro-3-(diethylamino)-6-methyl-1-phenyl-2(1*H*)-pyrazinone (5c).** To a solution of 2(1*H*)-pyrazinone **1c** (2.55 g, 10 mmol) in dry dioxane (200 mL) was added freshly distilled diethylamine (2.08 mL, 20 mmol), and the mixture was stirred for 2 h at 50 °C under nitrogen. The reaction mixture was cooled, the solvent was evaporated under reduced pressure, and the residual oil was dissolved in $CHCl_3$ (250 mL). The solution was washed two times with water (25 mL), dried over $MgSO_4$, and evaporated. Chromatographic purification on a silica gel column (10% EtOAc/$CHCl_3$) gave pyrazinone **5c** (2.68 g, 92%): mp 92 °C; IR (KBr) 1660, 1600 $cm^{-1}$; $^1H$ NMR $\delta$ 1.22 (t, 6 H), 1.89 (s, 3 H), 3.70 (q, 4 H), 7.10−7.60 (m, 5 H); $^{13}C$ NMR $\delta$ 13.6, 17.0, 44.2, 120.1, 124.7, 127.6, 128.9, 129.8, 138.5, 148.3, 152.4; MS *m*/*z* 291 ($M^+$), 276, 262, 248; exact mass calcd for $C_{15}H_{18}ClN_3O$ 291.1138, found 291.1144.

**3-(Diethylamino)-1-phenyl-2(1*H*)-pyrazinone (5d).** A mixture of compound **1a** (554 mg, 2 mmol), 10% palladium on activated charcoal (100 mg), and $NaHCO_3$ (168 mg, 2 mmol) in dry methanol (25 mL) was degassed three times and stirred for 2 h under hydrogen (1 atm) at rt using a gas buret. The catalyst was removed by filtration over a Millipore filter. After evaporation of the solvent under reduced pressure, the residue was dissolved in $CHCl_3$ (100 mL). The solution was washed two times with water (25 mL), dried over $MgSO_4$, and evaporated to give compound **6d** as an oil (437 mg, 90%): IR 1665, 1600 $cm^{-1}$; $^1H$ NMR $\delta$ 1.25 (t, 6 H), 3.72 (q, 4 H), 6.55 (d, 1 H, $J$ = 5 Hz), 6.90 (d, 1 H, $J$ = 5 Hz), 7.40 (m, 5 H); $^{13}C$ NMR $\delta$ 13.6, 44.2, 117.5, 121.6, 126.0, 128.1, 129.1, 140.3, 151.9, 152.0; MS *m*/*z* 243 ($M^+$), 228, 214, 200; exact mass calcd for $C_{14}H_{17}N_3O$ 243.1372, found 243.1381.

**5-Chloro-3-(ethylamino)-1-methyl-2(1*H*)-pyrazinone (5e).** A solution of compound **1b** (1.55 g, 8.7 mmol), ethylamine hydrochloride (1.4 g, 17.4 mmol), and freshly distilled triethylamine (3 mL, 21.7 mmol) in dry $CHCl_3$ (125 mL) was stirred at rt for 1 week and then heated at 70 °C for 12 h. The reaction mixture was cooled, diluted with $CHCl_3$ (150 mL), and washed with 0.5 N HCl (2 × 20 mL) and water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude pyrazinone **5e** was chromatographed on an alumina column (gradient elution $CHCl_3$ → 5% EtOAc/$CHCl_3$). Crystallization from ethanol afforded the pure product **5e** (1.38 g, 85%): mp 92−93 °C; IR (KBr) 3350, 1670, 1605 $cm^{-1}$; $^1H$ NMR $\delta$ 1.20 (t, 3 H), 3.45 (s, 3 H), 3.50 (qd, 2 H), 6.55 (s, 1 H), 6.75 (s (br), 1 H); MS *m*/*z* 187 ($M^+$, 100), 172, 158, 144; exact mass calcd for $C_7H_{10}ClN_3O$ 187.0512, found 187.0512. Anal. Calcd for $C_7H_{10}ClN_3O$: C, 44.81; H, 5.37; N, 22.40. Found: C, 44.78; H, 5.42; N, 22.51.

**5-Chloro-3-(1*H*-indol-3-yl)-1-benzyl-2(1*H*)-pyrazinone (5g).** A 2 M solution of ethylmagnesium bromide (6 mL, 12 mmol) in THF was added under nitrogen to a stirred solution of indole (1.4 g, 12 mmol) in dry toluene (200 mL). The resulting mixture was heated at reflux for 2 h. The reaction mixture was cooled to rt, and a solution of 1-benzyl-3,5-dichloro-2(1*H*)-pyrazinone (**1d**) (2 g, 8 mmol) in dry toluene (50 mL) was added. The mixture was heated at reflux for 2 h and subsequently stirred overnight at rt. A 10% $NH_4Cl$ solution (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined organic fractions were washed with water (2 × 50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated, and the crude product **5g** was chromatographed on a silica gel column using gradient elution (10% EtOAc/$CHCl_3$ → 40% EtOAc/$CHCl_3$). Crystallization from ethanol gave pure **5g** (1.49 g, 56%): mp 188 °C; IR (KBr) 1645, 1575 $cm^{-1}$; $^1H$ NMR $\delta$ 5.10 (s, 2 H), 7.00 (s, 1 H), 7.20−7.40 (m, 8 H), 8.75 (m, 2 H), 8.95 (s, 1 H); $^{13}C$ NMR $\delta$ 52.5, 111.5, 112.5, 120.3, 122.0, 123.2, 123.4, 127.1, 126.1, 128.3, 128.6, 129.1, 132.2, 134.8, 136.0, 150.4, 154.0; MS *m*/*z* 335 ($M^+$), 244, 216, 91; exact mass calcd for $C_{19}H_{14}ClN_3O$ 335.0825, found 335.0827. Anal. Calcd for $C_{19}H_{14}ClN_3O$: C, 67.96; H, 4.20; N, 12.51. Found: C, 67.57; H, 4.10; N, 12.31.

**General Procedure for the Synthesis of Compounds 12-19 and 21-27.** A solution of 3-amino-2(1*H*)-pyrazinone (**5a**−**g**) (1 mmol) and a dienophile (3 mmol) in freshly distilled toluene (10 mL) [dry pyridine (10 mL) was used for the products **15**, **16**, **23**−**25**, and **27**] was stirred under the conditions (temperature and reaction time) indicated below. The solvent was evaporated *in vacuo*, and the residue was purified by chromatography on a silica gel column (gradient elution 100% $CHCl_3$ → 10% EtOAc/$CHCl_3$).

**Methyl 6-Cyano-1,2-dihydro-2-oxo-1-phenyl-4-pyridinecarboxylate (12a).** Reaction of **5a** and methyl acrylate following the general procedure (toluene 80 °C, 1 d) gave **12a** (201 mg, 79%). Treatment of **15a** in toluene with dry HCl and further heating of the precipitated salt for 5 min also afforded compound **12a**: mp 178−179 °C; IR (KBr) 2225, 1735, 1685 $cm^{-1}$; $^1H$ NMR $\delta$ 4.00 (s, 3 H), 7.26 (d, 1 H, $J$ = 2 Hz), 7.32 (m, 2 H), 7.50 (d, 1 H, $J$ = 2 Hz), 7.55 (m, 3 H); $^{13}C$ NMR $\delta$ 53.3, 111.7, 113.5, 122.3, 129.2, 127.4, 129.9, 130.3, 136.8, 139.6, 160.7, 163.1; MS *m*/*z* 254 ($M^+$), 253, 239, 195, 77; exact mass calcd for $C_{14}H_{10}N_2O_3$ 254.0691, found 254.0683. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.04; H, 3.88; N, 10.97.

**Methyl 6-Cyano-1,2-dihydro-1-methyl-2-oxo-4-pyridinecarboxylate (12b).** Reaction of **5b** and methyl acrylate following the general procedure (toluene, 80 °C, 1 d) gave **12b** (163 mg, 85%): mp 143−144 °C; IR (KBr) 2235, 1740, 1670 $cm^{-1}$; $^1H$ NMR $\delta$ 3.75 (s, 3 H), 3.97 (s, 3 H), 7.22 (d, 1 H, $J$ = 2 Hz), 7.42 (d, 1 H, $J$ = 2 Hz); MS *m*/*z* 192 ($M^+$), 160, 133; exact mass calcd for $C_9H_8N_2O_3$ 192.0535, found 192.0533. Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.92; H, 4.22; N, 14.53.

**Methyl 6-Cyano-3-(diethylamino)-1,2,5,6-tetrahydro-6-methyl-2-oxo-1-phenyl-4-pyridinecarboxylate (13) and Methyl 3-(Diethylamino)-1,2-dihydro-6-methyl-2-oxo-1-phenyl-4-pyridinecarboxylate (14).** Reaction of **5c** and methyl acrylate following the general procedure (toluene, 80 °C, 1 d) gave **13** (140 mg, 41%) as a colorless and unstable oil: IR (film) 2225, 1710, 1665 $cm^{-1}$; $^1H$ NMR $\delta$ 1.10 (t, 6 H), 1.42 (s, 3 H), 2.95 (d, 1 H, $J$ = 17 Hz), 3.15 (d, 1 H, $J$ = 17 Hz), 3.25 (q, 4 H), 3.82 (s, 3 H), 7.40 (m, 5 H); $^{13}C$ NMR $\delta$ 13.8, 26.3, 38.5, 47.2, 51.8, 112.2, 120.6, 127.5, 128.8, 129.6, 137.6, 145.7, 163.1, 166.1; MS *m*/*z* 341 ($M^+$), 326, 310, 299; exact mass calcd for $C_{19}H_{23}N_3O_3$ 341.1740, found 341.1736.

When the reaction was carried out at reflux (toluene, 2 d), compound **14** was obtained in 83% yield calculated on the basis of **5c**. The isolated compound **13** was subjected to the same conditions (toluene, reflux for 2 d) to afford compound **14** in quantitative yield. The spectral characteristics of **14** were identical to those of the product obtained from the reaction of **5c** with methyl propynoate.[6]

**Methyl 6-Cyano-3-(diethylamino)-1,2,5,6-tetrahydro-1-phenyl-2-oxo-4-pyridinecarboxylate (15a).** Reaction of **5a** with methyl acrylate following the general procedure (pyridine, 80 °C, 10 h) gave **15a** (235 mg, 72%) as an unstable oil: IR (film) 1725, 1680 $cm^{-1}$; $^1H$ NMR $\delta$ 1.15 (t, 6 H), 3.01 (dd, 1 H, $J$ = 17, 3 Hz), 3.18 (dd, 1 H, $J$ = 17, 5 Hz), 3.15−3.45 (m, 4 H), 3.80 (s, 3 H), 4.65 (dd, 1 H, $J$ = 5, 3 Hz), 7.20−7.60 (m, 5 H); $^{13}C$ NMR $\delta$ 13.6, 29.6, 47.0, 50.0, 51.7, 111.1, 117.7, 125.8−129.5, 140.5, 145.9, 161.6, 165.8; MS *m*/*z* 327 ($M^+$), 312, 255, 77; exact mass calcd for $C_{18}H_{21}N_3O_3$ 327.1582, found 327.1576.

**Methyl 6-Cyano-3-(diethylamino)-1,2,5,6-tetrahydro-1-methyl-2-oxo-4-pyridinecarboxylate (15b).** Reaction of **5b** with methyl acrylate following the general procedure gave **15b** (207 mg, 78%) as an unstable oil: IR (film) 2240, 1700, 1670 $cm^{-1}$; $^1H$ NMR $\delta$ 1.09 (t, 6 H), 2.91 (dd, 1 H, $J$ = 17, 6 Hz), 3.03 (dd, 1 H, $J$ = 17, 7 Hz), 3.13 (s, 3 H), 3.11−3.38 (m, 4 H), 3.79 (s, 3 H), 4.30 (dd, 1 H, $J$ = 5, 3 Hz); $^{13}C$ NMR $\delta$ 13.5, 28.6, 34.6, 46.9, 48.8, 51.7, 111.8, 117.1, 145.6, 162.5, 166.2; MS *m*/*z* 265 ($M^+$), 250, 219, 190; exact mass calcd for $C_{13}H_{19}N_3O_3$ 265.1426, found 265.1424.

**Methyl 3-(Diethylamino)-1,2-dihydro-2-oxo-1-phenyl-4-pyridinecarboxylate (16a).** Reaction of **5a** with methyl acrylate following the general procedure (pyridine, reflux, 2 d) gave **16a** (210 mg, 70%): mp 91−92 °C; IR (KBr) 1740, 1660 $cm^{-1}$; $^1H$ NMR $\delta$ 1.06 (t, 6 H), 3.23 (q, 4 H), 3.90 (s, 3 H), 6.28 (d, 1 H, $J$ = 7.5 Hz), 7.10 (d, 1 H, $J$ = 7.5 Hz), 7.35−7.50 (m,

5 H); $^{13}$C NMR $\delta$ 13.9, 46.3, 52.2, 104.5, 126.6, 128.4, 129.2, 131.3, 133.6, 140.7, 140.8, 161.4, 167.5; MS *m/z* 300 ($M^+$), 285, 271, 257, 230, 77; exact mass calcd for $C_{17}H_{20}N_2O_3$ 300.1474, found 300.1480.

**Methyl 3-(Diethylamino)-1,2-dihydro-1-methyl-2-oxo-4-pyridinecarboxylate (16b).** Reaction of **5b** with methyl acrylate following the general procedure (pyridine, reflux, 2 d) gave **16b** (oil, 180 mg, 75%): IR (film) 1737, 1650 cm$^{-1}$; $^1$H NMR $\delta$ 1.03 (t, 6 H), 3.20 (q, 4 H), 3.55 (s, 3 H), 3.85 (s, 3 H), 6.20 (d, 1 H, $J$ = 7 Hz), 7.05 (d, 1 H, $J$ = 7 Hz); $^{13}$C NMR $\delta$ 13.8, 37.5, 46.1, 52.0, 104.0, 132.0, 134.7, 139.6, 161.8, 167.4; MS *m/z* 238 ($M^+$), 223, 209; exact mass calcd for $C_{12}H_{18}N_2O_3$ 238.1317, found 238.1316.

**Methyl 6-Cyano-3-(ethylamino)-1,2,5,6-tetrahydro-1-methyl-2-oxo-4-pyridinecarboxylate (17).** Reaction of **5e** with methyl acrylate following the general procedure (toluene, 80 °C, 5 d) gave **17** (190 mg, 80%) as an unstable oil: IR 2250, 1730, 1675 cm$^{-1}$; $^1$H NMR $\delta$ 1.21 (t, 3 H), 2.85 (dd, 1 H, $J$ = 18, 6 Hz), 3.00 (dd, 2 H, $J$ = 18, 3 Hz), 3.13 (s, 3 H), 3.40−3.80 (m, 4 H), 3.75 (s, 3 H), 4.32 (dd, 1 H, $J$ = 6, 3 Hz), 8.30 (s, 1 H); $^{13}$C NMR $\delta$ 16.1, 26.0, 34.2, 40.2, 49.1, 51.1, 91.3, 117.2, 146.6, 160.3, 168.9; MS *m/z* 237 ($M^+$), 220, 205, 190, 177; exact mass calcd for $C_{11}H_{15}N_3O_3$ 237.1113, found 237.1116.

**Methyl 3-Amino-6-cyano-1,2,5,6-tetrahydro-1-methyl-2-oxopyridine-4-carboxylate (18).** Reaction of **5f** and methyl acrylate following the general procedure (toluene, 110 °C, 3 d) gave **18** (134 mg, 64%): mp 134−135 °C; IR 2240, 1730, 1665 cm$^{-1}$; $^1$H NMR $\delta$ 2.90 (dd, 1 H), 3.00 (dd, 1 H), 3.18 (s, 3 H), 3.79 (s, 3 H), 4.38 (dd, 1 H), 8.00 (s, 2 H); $^{13}$C NMR $\delta$ 25.1, 34.6, 49.1, 51.4, 91.3, 116.9, 143.0, 161.2, 168.8; MS *m/z* 209 ($M^+$), 178, 150, 141; exact mass calcd for $C_9H_{11}N_3O_3$ 209.0800, found 209.0802. Anal. Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.30; H, 5.25; N, 19.90.

**3-(6-Cyano-1,2,5,6-tetrahydro-2-oxo-1-benzylpyridin-3-yl)indole (19).** A solution of 2(1*H*)-pyrazinone **5g** (200 mg, 0.6 mmol) in dry toluene (30 mL) was made to react with ethene (25 atm) in a steel vessel. The mixture was stirred at 110 °C for 3 d. The gas was removed carefully, and the solvent was evaporated under reduced pressure. Flash chromatography and subsequent HPLC chromatography on silica gel (10% EtOAc/$CHCl_3$) gave **19** (135 mg, 70%) as an unstable oil. This was crystallized from a hexane/$CHCl_3$ mixture: mp 58 °C; IR (KBr) 3295, 1650, 1610 cm$^{-1}$; $^1$H NMR $\delta$ 2.75 (ddd, 1 H, $J$ = 17.5, 6.25, 2.2 Hz), 2.90 (ddd, 1 H, $J$ = 17.5, 6.25, 2.8 Hz), 4.15 (d, 1 H, $J$ = 15 Hz), 4.40 (ddd, 1 H, $J$ = 6.25, 2.2, 0.9 Hz), 5.55 (d, 1 H, $J$ = 15 Hz), 6.92 (ddd, 1 H, $J$ = 6.25, 2.8, 0.9 Hz), 7.1−7.45 (m, 8 H), 7.78 (m, 1 H), 7.82 (d, 1 H, $J$ = 4.5 Hz), 8.35 (br s, 1 H); $^{13}$C NMR $\delta$ 28.1, 46.0, 49.2, 110.7, 111.4, 117.2, 119.6, 120.5, 122.3, 126.1, 128.3, 128.5, 128.6, 129.1, 129.1, 130.1, 136.1, 163.8; MS *m/z* 327 ($M^+$), 300, 91; exact mass calcd for $C_{21}H_{17}N_3O$ 327.1370, found 327.1370.

**3-(1,2-Dihydro-2-oxo-1-benzylpyridin-3-yl)indole (20).** The crude compound **19** was treated with an aqueous 1 N NaOH/dioxane solution (40 mL, 1:1), and the mixture was further stirred for 3 h. Water (40 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by using preparative TLC (silica gel, 10% EtOAc/$CHCl_3$). Crystallization from $CCl_4$ gave the analytical sample **20** (155 mg, 86%): mp 174 °C; IR (KBr) 3280, 1645, 1585 cm$^{-1}$; $^1$H NMR $\delta$ 5.30 (s, 2 H), 6.33 (t, 1 H, $J$ = 7 Hz), 7.10−7.40 (m, 9 H), 7.91 (m, 2 H), 8.20 (d, 1 H, $J$ = 2.8 Hz), 8.75 (br s, 1 H); $^{13}$C NMR $\delta$ 52.7, 106.5, 111.2, 111.6, 119.6, 120.2, 122.0, 125.9, 126.8, 126.9, 127.8, 128.1, 128.8, 133.4, 134.0, 136.1, 161.5; MS *m/z* 300 ($M^+$), 209, 181, 91; exact mass calcd for $C_{20}H_{16}N_2O$ 300.1262, found 300.1270.

**1,6-Dihydro-1,4-diphenyl-6-oxo-2-pyridinecarbonitrile (21).** Reaction of **5a** and styrene following the general procedure (toluene, 80 °C, 7 d) gave **21** (207 mg, 76%): mp 180−181 °C; IR (KBr) 2235, 1670 cm$^{-1}$; $^1$H NMR $\delta$ 7.20−7.50 (m, 12 H); $^{13}$C NMR $\delta$ 112.3, 115.2, 121.7, 123.0, 125.2, 126.5, 127.7, 128.6, 129.4, 129.7, 130.0, 135.2, 137.1, 150.5; MS *m/z* 272 ($M^+$), 244, 77; exact mass calcd for $C_{18}H_{12}N_2O$ 272.0950, found 272.0941. Anal. Calcd for $C_{18}H_{12}N_2O$: C, 76.40; H, 4.44; N, 10.29. Found: C, 76.76; H, 4.35; N, 9.95.

**Dimethyl 2-Cyano-1,6-dihydro-6-oxo-1-phenyl-3,4-pyridinedicarboxylate (22).** Reaction of **5a** and dimethyl maleate following the general procedure (toluene, 80 °C, 3 d) gave **22** (275 mg, 88%): mp 157−158 °C; IR (KBr) 2230, 1730, 1680 cm$^{-1}$; $^1$H NMR $\delta$ 3.85 (s, 6 H), 7.10 (s, 1 H), 7.50 (m, 5 H); MS *m/z* 312 ($M^+$), 297, 281, 253; exact mass calcd for $C_{16}H_{12}N_2O_5$ 312.0746, found 312.0747. Anal. Calcd for $C_{16}H_{12}N_2O_5$: C, 61.54; H, 3.87; N, 8.97. Found: C, 61.54; H, 3.80; N, 8.91.

**5-(Diethylamino)-1,2,3,6-tetrahydro-1,4-diphenyl-6-oxo-2-pyridinecarbonitrile (23).** Reaction of **5a** with styrene following the general procedure (pyridine, reflux, 2 d) gave a mixture of **23** (163 mg, 50%) and **24** (32 mg, 10%). Compound **23** was obtained as an unstable oil after purification on a silica gel preparative plate, eluting with $CH_2Cl_2$: IR (film) 1663 cm$^{-1}$; $^1$H NMR $\delta$ 0.97 (t, 6 H), 2.78−3.05 (m, 4 H), 2.83 (dd, 1 H, $J$ = 17, 2 Hz), 3.52 (dd, 1 H, $J$ = 17, 5 Hz), 4.72 (dd, 1 H, $J$ = 5, 2 Hz), 7.20−7.60 (m, 10 H); $^{13}$C NMR $\delta$ 13.8, 34.1, 47.2, 50.1, 118.2, 125.9, 127.6, 127.6, 128.0, 128.1, 129.5, 137.8, 137.9, 138.7, 140.7, 162.8; MS *m/z* 345 ($M^+$), 330, 316; exact mass calcd for $C_{22}H_{23}N_3O$ 345.1842, found 345.1846.

**3-(Diethylamino)-1,4-diphenyl-2(1*H*)-pyridinone (24).** Reaction of **5a** and styrene following the general procedure (pyridine, reflux, 8 d) gave **24** (127 mg, 40%): mp 99−101 °C; IR (KBr) 1647 cm$^{-1}$; $^1$H NMR $\delta$ 0.91 (t, 6 H), 3.02 (q, 4 H), 6.21 (d, 1 H, $J$ = 7 Hz), 7.20 (d, 1 H, $J$ = 7 Hz), 7.45 (m, 10 H); $^{13}$C NMR $\delta$ 13.8, 46.4, 108.5, 126.7, 127.6, 127.9, 128.1, 128.6, 129.2, 132.4, 138.0, 139.3, 141.1, 146.9, 162.2; MS *m/z* 318 ($M^+$), 303, 289; exact mass calcd for $C_{21}H_{22}N_2O$ 318.1732, found 318.1729.

**Dimethyl 5-(Diethylamino)-1,6-dihydro-6-oxo-1-phenyl-3,4-pyridinedicarboxylate (25).** Reaction of **5a** and dimethyl maleate following the general procedure (pyridine, 80 °C, 3 d) gave **25** (268 mg, 75%). This compound showed the same spectral characteristics as the product isolated from the reaction of **5a** with dimethyl butynedioate.[6]

**2,3,5,6-Tetrahydro-5-methyl-2-phenyl-1,3,6-trioxo-1*H*-pyrrolo[3,4-*c*]pyridine-4-carbonitrile (26).** Reaction of **5b** and *N*-phenylmaleimide following the general procedure (toluene, 80 °C, 15 h) gave **26** (254 mg, 91%): mp 258−259 °C (hexane/acetone); IR (KBr) 2240, 1725, 1650 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 3.80 (s, 3 H), 7.30 (s, 1 H), 7.50 (m, 5 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 35.0, 109.6, 114.0, 118.7, 119.4, 127.1, 128.7, 128.9, 131.2, 139.6, 161.0, 162.1, 163.2; MS *m/z* 279 ($M^+$), 250, 223; exact mass calcd for $C_{15}H_9N_3O_3$ 279.0644, found 279.0635. Anal. Calcd for $C_{15}H_9N_3O_3$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.10; H, 3.10; N, 14.73.

**7-(Diethylamino)-5-methyl-2-phenyl-1*H*-pyrrolo[3,4-*c*]-pyridine-1,3,6(2*H*,5*H*)-trione (27).** Reaction of **5b** and *N*-phenylmaleimide following the general procedure (pyridine, 20 °C, 15 h) gave **27** (283 mg, 87%): mp 140−141 °C; IR (KBr) 1710, 1650 cm$^{-1}$; $^1$H NMR $\delta$ 1.20 (s, 6 H), 3.50 (s, 3 H), 3.70 (q, 4 H), 7.40 (m, 5 H), 7.70 (s, 1 H); MS *m/z* 325, 310, 296, 282, 267; exact mass calcd for $C_{18}H_{19}N_3O_3$ 325.1426, found 325.1419. Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.32; H, 5.83; N, 12.79.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra for **5c**, **5d**, **15a**, **15b**, **16a**, **16b**, **17**, **19**, **20**, **23**, and **24** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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