Transformations of (*Z*)-2-benzoylamino-4-dimethylamino-2-oxo-3-butene and (*E*)-3-benzoylamino-4-cyano-2-oxo-3-butene into pyrimidine, pyrazole and isoxazole derivatives

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Dedicated to Professor Gábor Bernáth, University of Szeged, on his 70th Anniversary

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Abstract

Reaction of (*Z*)-2-Benzoylamino-4-dimethylamino-2-oxo-3-butene **1** with amidines **2a–e** afforded pyrimidines **3a–e**. Acid-catalysed treatment of **1** with potassium cyanide gave (*E*)-3-benzoylamino-4-cyano-2-oxo-3-butene **4**. 1,3-Dipolar cycloadditions of nitrile imines and 2,4,6-trimethoxybenzonitrile oxide **7a** to compound **4** afforded the corresponding pyrazole derivatives **6a–d** and the isoxazole-4-carbonitrile **8a**. In the reaction of **4** with 2,4,6-trimethylbenzonitrile oxide **7b**, bis-cycloadduct **9** was formed and its structure was also determined by X-Ray analysis.

Keywords: Heterocycles, *N*,*N*-dimethylenaminones, acrylonitriles, cyclocondensations, cycloadditions

Introduction

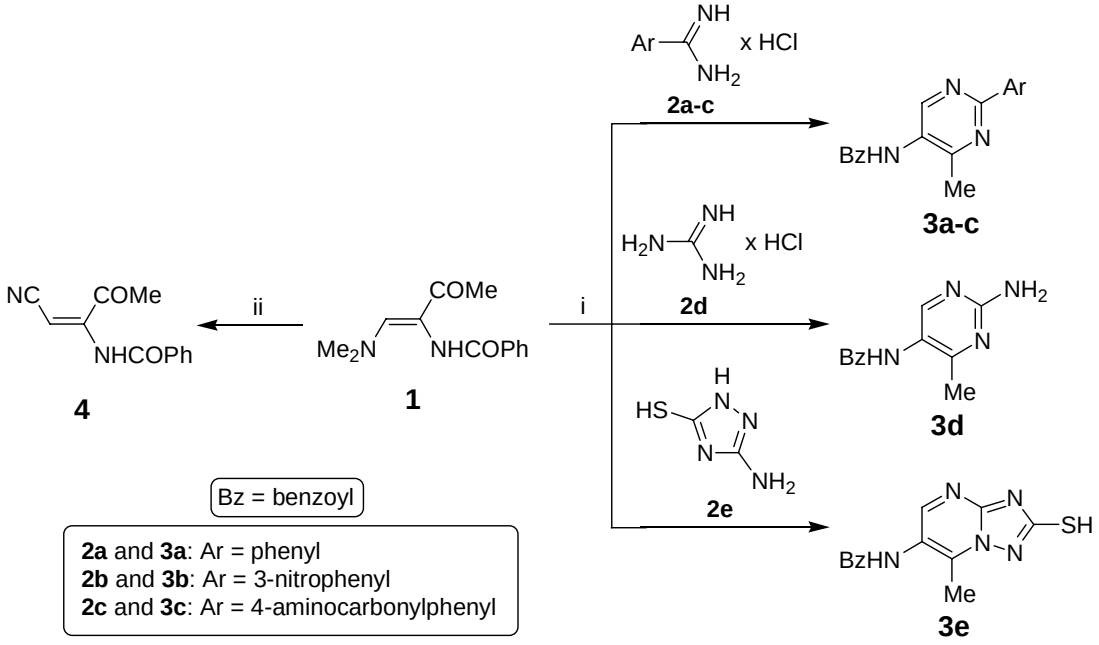
Enaminones,[1] such as β-dimethylamino derivatives of α,β-unsaturated ketones, esters, and nitriles, are an important class of compounds, which have been used extensively for the preparation of a variety of heterocyclic systems[1,2] including some natural products and analogues.[3] Recently, β-dimethylamino-α,β-unsaturated ketones and nitriles have been transformed into pyridine, isoquinoline,[4] pyrazole, isoxazole, pyrimidine,[5] and pyranone derivatives.[6]

In this connection, we have previously reported a 3 step preparation of (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene **1** from hippuric acid and cyclizations of the enaminone **1** into pyrazole and pyrido[2,3-*d*]pyrimidine derivatives. Structural determination of **1** and two of its dimethylamine substitution products has also been performed using 2D NMR (HMBC techique). In all cases, the (*Z*)-configuration around the C=C double bond has been established.[7]

As an extension of these studies we describe here some applications of (*Z*)-2-benzoylamino-4-dimethylamino-2-oxo-3-butene **1** and (*E*)-3-benzoylamino-4-cyano-2-oxo-3-butene **2** in the synthesis of heterocyclic systems.

Results and Discussion

(*Z*)-3-Benzoylamino-4-dimethylamino-2-oxo-3-butene **1** has been prepared in 3 steps from hippuric acid in 58 % yield.[7] Compound **1**, when treated with amidines **2a–c** in ethanol in the presence of sodium carbonate, produced 2-aryl-5-benzoylamino-4-methylpyrimidines **3a–c**. The following amidines were selected: benzamidine hydrochloride **2a**, 4-amidinobenzamide hydrochloride **2b**, and 3-nitrobenzamidine hydrochloride **2c**. Similarly, enaminone **1** reacted with amidine like compounds, such as guanidine hydrochloride **2d** and 3-amino-5-mercapto-1*H*-1,2,4-triazole **2e** to give the corresponding 2-aminopyrimidine derivative **3d** and 6-benzoylamino-2-mercapto-7-methyl-[1,2,4]triazolo[1,5–*a*]pyrimidine **3e**, respectively. The compounds exhibit a signal for the 4–Me group at δ = 2.18–2.58 ppm, several multiplets at δ = 7.54–8.80 ppm for protons attached to the aromatic rings, a singlet at δ = 8.04–8.97 ppm for 6–H, two exchangable protons at δ = 7.44 ppm for the NH_2 group attached at 2-position of **3b**, and one exchangable proton at δ = 10.28–10.52 ppm for the NHCO group. The dimethylamino group in (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene **1** can be exchanged by a cyano group with potassium cyanide in a mixture of toluene and acetic acid under reflux to give (*E*)-3-benzoylamino-4-cyano-2-oxo-3-butene **4** in 72% yield (Scheme 1).



Scheme 1. Reagents end conditions: (i) compound **2**, EtOH, Na_2CO_3, reflux; (ii) KCN, toluene, AcOH, reflux.

The structure of nitrile **4** was confirmed by spectroscopic methods and by microanalysis for C, H, and N. The ^{1}H NMR spectrum shows a singlet at δ = 2.88 ppm for the methyl group, two multiplets at δ = 7.49–7.64 ppm and δ = 7.82–7.86 ppm for the protons of benzoyl group, and a singlet at δ = 7.83 ppm for the proton attached to the C=C double bond. The IR spetrum exhibits a peak at ν = 2200 cm^{-1}, characteristic for a cyano group. Since compound **4** was isolated as a single isomer, differentiation between (*Z*)- and (*E*)-form can be easily achieved on the basis of the magnitude of the long-range heteronuclear coupling constants, $^3J_{C–H}$, which have been used previously for the determination of conformations and configurations of various *α,β*-unsaturated systems.[8–10] Recently, the orientation around the C=C double bond in alkyl 2,3-diaminopropenoates has been determined using a 2D HMBC method.[11] Generally, the magnitude of the coupling constants $^3J_{C–H}$ for nuclei with a (*Z*)-orientation around the C=C double bond are smaller (2–6 Hz) than those for the (*E*)-oriented ones (8–12 Hz).[11,12] Similar coupling constants have also been observed in some oxazolone derivatives with an analogous structural element.[13,14] The HMBC correlation technique has been found to be the most suitable for the determination of the configuration around the C=C double bond in analogous compounds.[3,7,15] Thus, in the case of compound **4**, the magnitude of the heteronuclear coupling constant, $^3J_{C–H}$ = 10.1 Hz, clearly indicates the (*E*)-orientation (Figure 1).

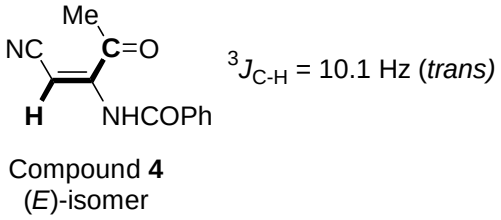
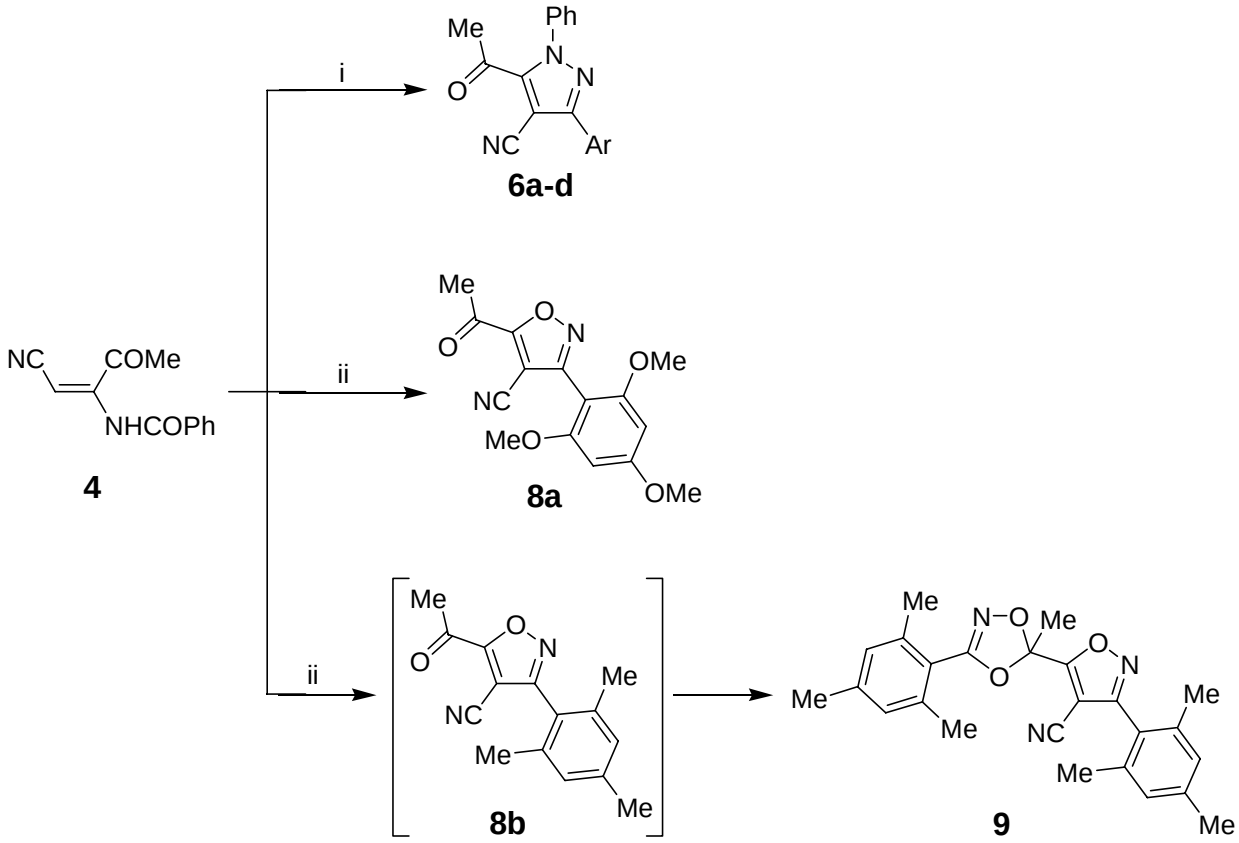


Figure 1

Since the C=C double bond in compound **4** is activated, some 1,3-dipolar cycloadditions of nitrile imines and nitrile oxides were studied. For this purpose *N*-phenylbenzohydrazonoyl chlorides **5a–d** were selected. The reactions were carried out in boiling dichloromethane, in the presence of triethylamine in order to achieve the *in situ* formation of the corresponding nitrile imines, producing 5-acetyl-4-cyano-3-aryl-1-phenyl-1*H*-pyrazoles **6a–d** in 53–75% yields. The structure of compounds **6a–d** were determined on the basis of elemental analyses for C, H, and N, and IR spectra, which show a band at ν = 2250–2300 cm^{-1} characteristic for a cyano group, similarly as shown in other cyano propenoates prepared in our laboratory.[15a,d,e,16,17] By 1,3-dipolar cycloadditions of benzonitrile oxides **7a,b** to compound **4** two types of products were formed. When compound **4** was heated for 6 h in dichloromethane with 2,4,6-trimethoxybenzonitrile oxide **7a**, the corresponding 5-acetyl-4-cyano-3-(2,4,6-trimethoxyphenyl)-isoxazole **8a** was isolated in 47% yield. On the other hand, when the reaction was carried out with 2,4,6-trimethylbenzonitrile oxide **7b**, a cycloadduct **9** resulting by

cycloaddition of 2 molecules of nitrile oxide **7b** to one molecule of **4** was isolated in 34% yield. This is clearly visible from the ^{1}H NMR spectrum in which peaks for two 2,4,6-trimethylphenyl groups are present. Since the IR spectrum exhibits a signal at ν = 2240 cm^{-1} characteristic for the cyano group, the most plausible explanation is that first the mono-cycloadduct **8b** is formed and then the second cycloaddition of nitrile oxide is taking place to the C=O double bond of the 5-acetyl group (Scheme 2).



Scheme 2. Reagents and conditions: (i) Ar–C(Cl)=NNHPh **5a–d** (**4**:**5** in equimolar ratio), Et_3N, CH_2Cl_2, reflux; (ii) Ar–C≡N$^+$–O$^-$ **7a,b** (**4**:**7** in equimolar ratio), CH_2Cl_2, reflux.

This was also confirmed by X-ray analysis which shows the compound **9** to be 4-cyano-5-[5-methyl-3-(2,4,6-trimethylphenyl)-1,2,4-dioxazolyl-5]-3-(2,4,6-trimethyl-phenyl)isoxazole (Figure 2).

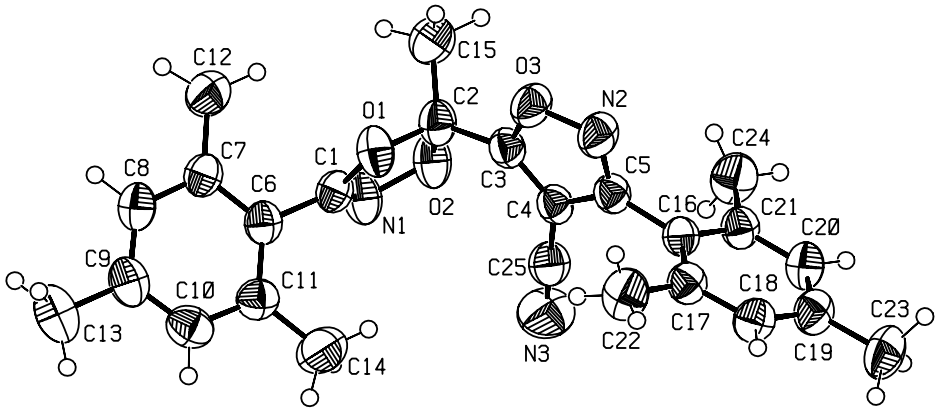


Figure 2. The asymmetric unit of compound **9** showing atom labels of the non-hydrogen atoms. Ellipsoids are plotted at a 50% probability level.

Experimental Section

General Procedures. Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra (300 MHz) were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with $CDCl_3$ and DMSO-d_6 as solvent and TMS as the internal standard. Mass spectra were obtained on an Autospeck Q spectrometer. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN *Analyser* 2400. All starting materials were commercially available (in most cases from *Fluka*). (*Z*)-2-Benzoylamino-4-dimethylamino-2-oxo-3-butene **1**,[7] benzohydrazonoyl chlorides **5a–d**,[23] and nitrile oxides **7a,b**[24] were prepared according to the published procedures.

General procedure for the preparation of 2-substituted 5-benzoylamino-4-methyl-pyrimidines (3a–d). A mixture of **1** (0.232 g, 1 mmol), amidine hydrochloride **2a–d** (1.5 mmol), ethanol (3 mL), and sodium carbonate (0.075–0.138 g, 0.7–1.3 mmol) was heated under reflux for 5–12 hours. Volatile components were evaporated *in vacuo*, the residue was triturated with water, and the precipitate was collected by filtration to give **3a–d**. The following compounds were prepared in this manner:

5-Benzoylamino-4-methyl-2-phenylpyrimidine (3a). Prepared from **1**, bezamidine hydrochloride **2a** (0.235 g, 1.5 mmol), and potassium carbonate (0.075 g, 0.7 mmol), reflux for 6 hours: 0.159 g (55%); mp 159–161 °C (from methanol). ^{1}H NMR (DMSO-d_6): δ 2.55 (3H, s, CH_3), 7.50–7.69 (6H, m, 6H of Ph), 8.01–8.09 (2H, m, 2H of Ph), 8.35–8.45 (2H, m, 2H of Ph),

8.85 (1H, s, 6–H), 10.28 (1H, s, NH). *Anal*. Calcd for $C_{18}H_{15}N_3O$ (289.33): C, 74.72; H, 5.23; N, 14.52. Found: C, 75.02; H, 5.14; N, 14.35.

5-Benzoylamino-4-methyl-2-(3-nitrophenyl)pyrimidine (3b). Prepared from **1**, 3-nitrobenzamidine hydrochloride **2b** (0.302 g, 1.5 mmol), and potassium carbonate (0.106 g, 1 mmol), reflux for 5 hours: 0.154 g (45%); mp 198–201 °C. ^{1}H NMR (DMSO-d_6): δ 2.59 (3H, s, CH_3), 7.54–7.67 (3H, m, 3H of Ph), 7.85 (1H, m, 1H of Ar), 8.02–8.06 (2H, m, 2H of Ph), 8.38 (1H, m, 1H of Ar), 8.80 (1H, m, 1H of Ar), 8.97 (1H, s, 6–H), 9.14 (1H, m, 1H of Ar), 10.35 (1H, s, NH). *Anal*. Calcd for $C_{18}H_{14}N_4O_3$ (334.33) $\times^1/_3H_2O$: C, 63.52; H, 4.34; N, 16.46. Found: C, 63.39; H, 4.17; N, 16.59.

5-Benzoylamino-4-methyl-2-(4-amidophenyl)pyrimidine (3c). Prepared from **1**, 4-amidinobenz-amide hydrochloride **2c** (0.298 g, 1.5 mmol), and potassium carbonate (0.106 g, 1 mmol), reflux for 12 hours: 0.053 g (16%); mp 289–293 °C (from ethanol–water–toluene). ^{1}H NMR (DMSO-d_6): δ 2.56 (3H, s, CH_3), 7.44 (2H, br s, NH_2), 7.54–7.66 (3H, m, 3H of Ph), 8.00–8.05 (2H, m, 2H of Ph), 8.02 (2H, d, J = 8.3 Hz, 2H of Ar), 8.44 (2H, d, J = 8.3 Hz, 2H of Ar), 8.89 (1H, s, 6–H), 10.30 (1H, s, NH). *Anal*. Calcd for $C_{19}H_{16}N_4O_2$ (332.36): C, 68.66; H, 4.85; N, 16.86. Found: C, 68.43; H, 4.50; N, 16.92.

2-Amino-5-benzoylamino-4-methylpyrimidine (3d). Prepared from **1**, guanidine hydrochloride **2d** (0.145 g, 1.5 mmol), and potassium carbonate (0.138 g, 1.3 mmol), reflux for 9 hours: 0.188 g (82%); mp 227–228 °C (from methanol). ^{1}H NMR (DMSO-d_6): δ 2.18 (3H, s, CH_3), 6.52 (2H, s, NH_2), 7.47–7.63 (3H, m, 3H of Ph), 7.92–7.99 (2H, m, 2H of Ph), 8.04 (1H, s, 6–H), 9.78 (1H, s, NH). *Anal*. Calcd for $C_{12}H_{12}N_4O$ (228.25): C, 63.14; H, 5.30; N, 24.55. Found: C, 63.04; H, 5.29; N, 24.27.

6-Benzoylamino-2-mercapto-7-methyl-[1,2,4]triazolo[1,5–*a*]pyrimidine (3e). A mixture of 3-amino-1,2,4-triazole-5-thiol **2e** (0.119 g, 1 mmol), (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene **1** (0.232 g, 1 mmol), ethanol (3 mL), and hydrochloric acid (36%, 3 drops, ~1 mmol) was heated under reflux for 1 hour. The precipitate was, after cooling, collected by filtration to give **3e**: 0.160 g (56%); mp 256–260 °C. ^{1}H NMR (DMSO-d_6): δ 2.63 (3H, s, CH_3), 7.54–7.68 (3H, m, 3H of Ph), 8.01–8.05 (2H, m, 2H of Ph), 8.71 (1H, s, 6–H), 10.52 (1H, s, NH), 14.27 (1H, br s, SH). *Anal*. Calcd for $C_{13}H_{11}N_5OS$ (285.33): C, 54.72; H, 3.89; N, 24.55. Found: C, 54.94; H, 4.06; N, 24.40.

(*E*)-3-Benzoylamino-4-cyano-2-oxo-3-butene (4). Acetic acid (3 mL) was added dropwise to a mixture of (*Z*)-3-benzoylamino-4-dimethylamino-2-oxo-3-butene **1** (0.232 g, 0.001 mol) and potassium cyanide (0.072 g, 0.0011 mol) in dry toluene (3 mL) and the mixture was heated under reflux for 15 minutes. The volatile components were evaporated *in vacuo*, the residue was triturated with cold water (6 mL), and the precipitate was collected by filtration to give **4**: 0.155 g (72%); mp 108–111 °C (from *n*-heptane–ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 2.88 (3H, s, CH_3), 7.49–7.64 (3H, m, 3H of Ph), 7.82–7.86 (2H, m, 2H of Ph), 7.83 (1H, s, CH), 9.23 (1H, br s, NH). *Anal*. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.15; H, 4.77; N, 13.01.

General procedure for the preparation of 5-acetyl-3-aryl-1-phenyl-1*H*-pyrazole-4-carbonitriles (6a–d). Triethylamine (0.2 mL, ~2 mmol) was added to a mixture of *N*-phenylbenzohydrazonoyl chloride **5a–d** (1 mmol), (*E*)-3-benzoylamino-4-cyano-2-oxo-3-butene **4** (0.214 g, 1 mmol), and dichloromethane (3 mL) and the mixture was heated under reflux for 1.5–2.5 h. The volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **6a–d**. The following compounds were prepared in this manner:

5-Acetyl-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile (6a). Prepared from **4** and *N*-phenylbenzohydrazonoyl chloride **5a** (0.230 g, 1 mmol), reflux for 1.5 h: 0.175 g (61%); mp 137–139 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 2.66 (3H, s, CH_3), 7.39–7.44 (2H, m, 2H of Ph), 7.47–7.55 (6H, m, 6H of Ph), 8.02–8.07 (2H, m, 2H of Ph). *Anal*. Calcd for $C_{18}H_{13}N_3O$ (287.32): C, 75.25; H, 4.56; N, 14.63. Found: C, 75.55; H, 4.30; N, 14.59.

5-Acetyl-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6b). Prepared from **4** and *N*-phenyl-4-methylbenzohydrazonoyl chloride **5b** (0.244 g, 1 mmol), reflux for 2.5 h: 0.160 g (53%); mp 138–139 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 2.42 (3H, s, CH_3), 2.65 (3H, s, CH_3), 7.30 (2H, d, J = 7.9 Hz, 2H of Ar), 7.39–7.42 (2H, m, 2H of Ph), 7.49–7.53 (3H, m, 3H of Ph), 7.94 (2H, d, J = 7.9 Hz, 2H of Ar). *Anal*. Calcd for $C_{19}H_{15}N_3O$ (301.34): C, 75.73; H, 5.02; N, 13.94. Found: C, 75.93; H, 4.85; N, 13.80.

5-Acetyl-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6c). Prepared from **4** and *N*-phenyl-4-chlorobenzohydrazonoyl chloride **5c** (0.263 g, 1 mmol), reflux for 1.5 h: 0.241 g (75%); mp 155–156 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 2.65 (3H, s, CH_3), 7.38–7.42 (2H, m, 2H of Ph), 7.47 (2H, d, J = 8.7 Hz, 2H of Ar), 7.51–7.55 (3H, m, 3H of Ph), 8.00 (2H, d, J = 8.7 Hz, 2H of Ar). *Anal*. Calcd for $C_{18}H_{12}ClN_3O$ (321.76): C, 67.19; H, 3.76; N, 13.06. Found: C, 66.98; H, 3.65; N, 13.00.

5-Acetyl-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6d). Prepared from **4** and *N*-phenyl-4-methoxybenzohydrazonoyl chloride **5d** (0.260 g, 1 mmol), reflux for 1.5 hours: 0.225 g (71%); mp 155–156 °C (from ethanol). ^{1}H NMR ($CDCl_3$): δ 2.65 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 7.01 (2H, d, J = 9.0 Hz, 2H of Ar), 7.38–7.43 (2H, m, 2H of Ph), 7.49–7.54 (3H, m, 3H of Ph), 8.00 (2H, d, J = 9.0 Hz, 2H of Ar). *Anal*. Calcd for $C_{19}H_{15}N_3O_2$ (317.34): C, 71.91; H, 4.76; N, 13.24. Found: C, 72.29; H, 4.56; N, 13.21.

5-Acetyl-3-(2,4,6-trimethoxyphenyl)isoxazole-4-carbonitrile (8a). A mixture of 2,4,6-trimethoxybenzonitrile oxide **7a** (0.209 g, 1 mmol), (*E*)-3-benzoylamino-4-cyano-2-oxo-3-butene **4** (0.214 g, 1 mmol), and dichloromethane (3 mL) was heated under reflux for 6 h. The volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **8a**: 0.142 g (47%); mp 148–149 °C (from ethanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.72 (3H, s, CH_3), 3.82 (6H, s, 2'-OCH_3, 6'-OCH_3), 3.88 (3H, s, 4'-OCH_3) 6.21 (2H, s, 3'–H, 5'–H). *Anal*. Calcd for $C_{15}H_{14}N_2O_5$ (302.28): C, 59.60; H, 4.67; N, 9.27. Found: C, 59.91; H, 4.76; N, 9.22.

5-[5-Methyl-3-(2,4,6-trimethylphenyl)-1,4,2-dioxazol-5-yl]-3-(2,4,6-trimethylphenyl)-isoxazole-4-carbonitrile (9). A mixture of **4** (0.214 g, 0.001 mol), 2,4,6-trimethylbenzonitrile

oxide **7b** (0.322 g, 1 mmol), and dichloromethane (3 mL) was heated under reflux for 4 h. The volatile components were evaporated *in vacuo*, the residue was triturated with ethanol, and the precipitate was collected by filtration to give **9**: 0.141 g (34%); mp 113–114 °C (from ethanol); MS: *m/z* = 415 (M^+), 416 (MH^+). HRMS Calcd for $C_{25}H_{25}N_3O_3$: 415.188590; Found: 415.189592. ^{1}H NMR (DMSO-d_6): δ 2.08 (3H, s, CH_3),), 2.12 (3H, s, CH_3), 2.23 (6H, s, 2 × CH_3), 2.28 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.32 (3H, s, CH_3), 7.03 (2H, s, 2H of Ar), 7.09 (2H, s, 2H of Ar). *Anal*. Calcd for $C_{25}H_{25}N_3O_3$ (415.48): C, 72.27; H, 6.06; N, 10.11. Found: C, 72.39; H, 6.09; N, 10.59.

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Supporting information available

The crystal structure of 4-cyano-5-[5-methyl-3-(2,4,6-trimethylphenyl)-1,2,4-dioxazolyl-5]-3-(2,4,6-trimethylphenyl)isoxazole **9** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 205467.

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