*Chemistry of Heterocyclic Compounds, Vol. 45, No. 9, 2009*

# SYNTHESIS OF 9-AZOLYL-3-(4-PHENYL-4H-1,2,4-TRIAZOL-3-YL)-4H,8H-PYRANO-[2,3-*f*]CHROMENE-4,8-DIONES

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*The reaction of 6-ethyl-8-formyl-7-hydroxy-3-(4-phenyl-4H-1,2,4-triazol-3-yl)chromone with 2-azolylacetonitriles gave 8-iminopyrano[2,3-f]chromen-4-ones, whose acid hydrolysis led to pyrano-[2,3-f]chromene-4,8-diones containing azaheterocyclic substituents at C-3 and C-9.*

**Keywords:** 2-azolylacetonitriles, 8-formyl-7-hydroxychromones, pyrano[2,3-*f*]chromene-4,8-diones, condensation.

The pyrano[2,3-*f*]chromene-4,8-dione system contains fragments of coumarin and chromone, both pharmacophoric molecules. 2-Aryl, 3-aryl, and 2-hetaryl derivatives of this system have bactericidal activity [1, 2]. Methyl derivatives have been proposed as photo reagents for DNA [3].

The pyrano[2,3-*f*]chromene-4,8-dione system may be obtained starting from both coumarins by completion of the γ-pyrone ring [1, 2, 4-6] and from chromones by annelation of the α-pyrone ring [1, 3, 7-13]. Derivatives with hetaryl groups at C-2 were obtained by the former approach: by the condensation of *o*-hydroxyacetylcoumarins with hetaroyl chlorides and subsequent rearrangement and cyclization [2, 5]. Derivatives with hetaryl substituents at C-9 were obtained in our laboratory using the second approach by the reaction of 8-formyl-7-hydroxyisoflavones with hetarylacetonitriles [13]. 3-Hetaryl derivatives of this system have not yet been reported.

In order to extend the range of heterocyclic derivatives of pyrano[2,3-*f*]chromene-4,8-dione we synthesized products containing azaheterocyclic substituents at C-3 and C-9.

We used 6-ethyl-8-formyl-7-hydroxy-3-(4-phenyl-4H-1,2,4-triazol-3-yl)chromone (**1**) [14], which already has a heterocycle at C-3, as the starting compound. Chromone **1** was obtained by two methods: 1) formylation of 6-ethyl-7-hydroxy-3-(4-phenyl-4H-1,2,4-triazol-3-yl)chromone (**2**) using the Duff reaction and 2) heating the corresponding 8-diethylaminomethyl derivative **3** [15] in acetic acid at reflux in the presence of hexamethylenetetramine.

The $^1$H NMR spectrum of chromone **1** in DMSO-$d_6$ shows a singlet for the formyl proton at 10.54 ppm but lacks signals characteristic for the starting chromone **2** (6.91 ppm for H-8) and chromone **3** ($Et_2NCH_2$ group signals). The signal for the 7-OH group is shifted downfield by 2 ppm as a consequence of formation of an

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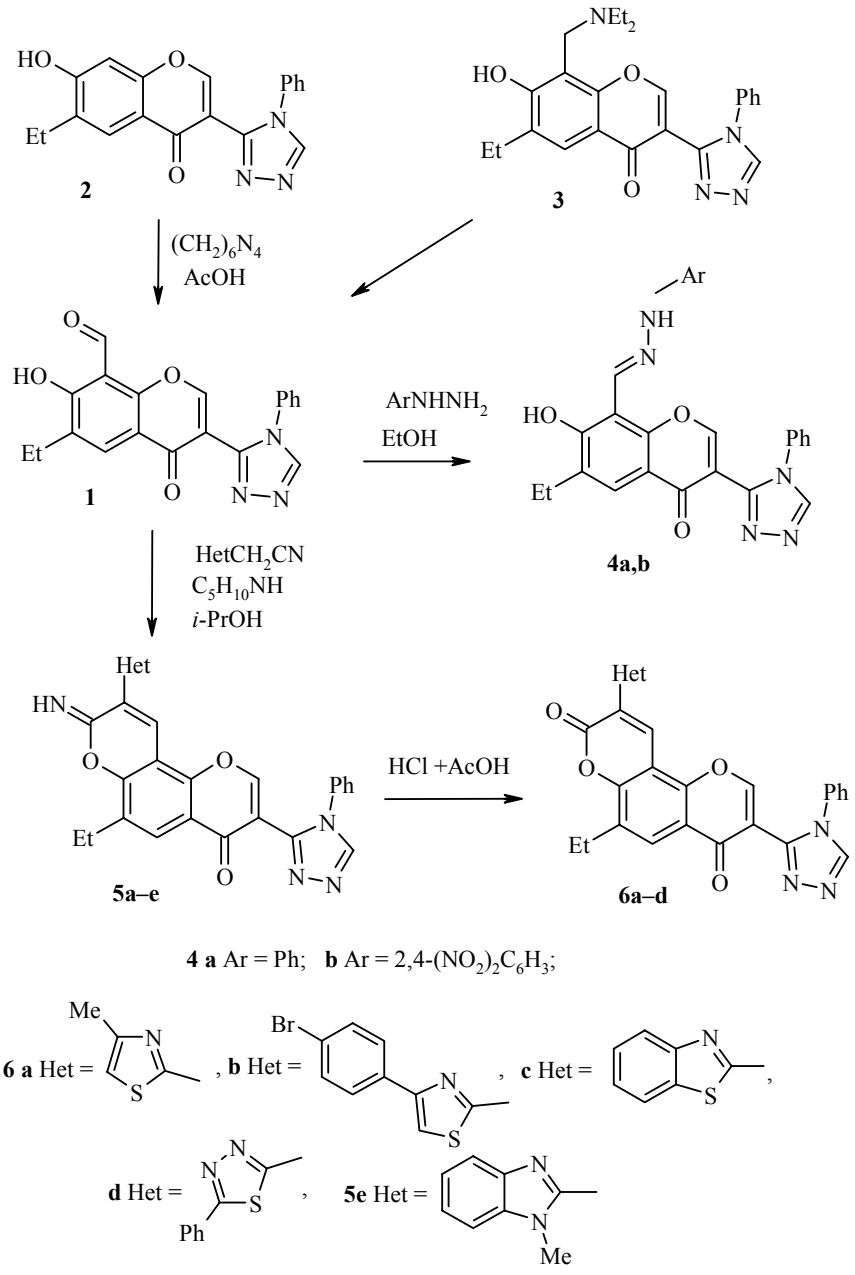
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1361-1367, September, 2009. Original article submitted February 13, 2008.

intramolecular hydrogen bond with the formyl group oxygen atom. The chelate structure of chromone **1** is indicated by its red-brown color in ethanolic ferric chloride [7, 16] and the broad IR band at 3080-3150 $cm^{-1}$. The formyl group C=O and chormone carbonyl stretching vibrations give rise to a strong band at 1645 $cm^{-1}$.




The reaction of chromone **1** with arylhydrazines in ethanol gives brightly colored, high-melting arylhydrazones **4a** and **4b**. The composition and structure of these products were confirmed by their elemental analysis and $^{1}H$ NMR spectra (Tables 1 and 2). The structure of hydrazone **4b** was additionally supported by analysis of the $^{13}C$ NMR DEPT spectra as well as HMQC and HMBC $^{13}C$-$^{1}H$ heteronuclear correlation spectra. As expected, the DEPT spectra with complete multiplicity editing have signals for one methyl group, one methylene group, and also ten nonequivalent CH signals (two of which have double intensity). The most

important of the correlations found in the HMBC spectrum are shown below by arrows. This result along with analysis of the 2D heteronuclear correlation spectra permitted the complete assignment of the carbon atom signals. The protonated carbon atoms were assigned using the HMQC spectra. Thus, it proved possible to obtain a complete assignment of the carbon atom signals in the spectrum of hydrazone **4b**.

The Knoevenagel reaction of chromone **1** with 2-cyanomethyl derivatives of 4-methyl-1,3-thiazole, 4-(4-bromophenyl)-1,3-thiazole, benzothiazole, 5-phenyl-1,3,4-thiadiazole, and 1-methylbenzimidazole in the presence of catalytic amounts of piperidine was used to synthesize 3,9-diazolylpyrano[2,3-*f*]chromene-4,8-diones. Carrying out this reaction in ethanol permitted us to isolate previously unreported 8-imino derivatives of this system **5**.

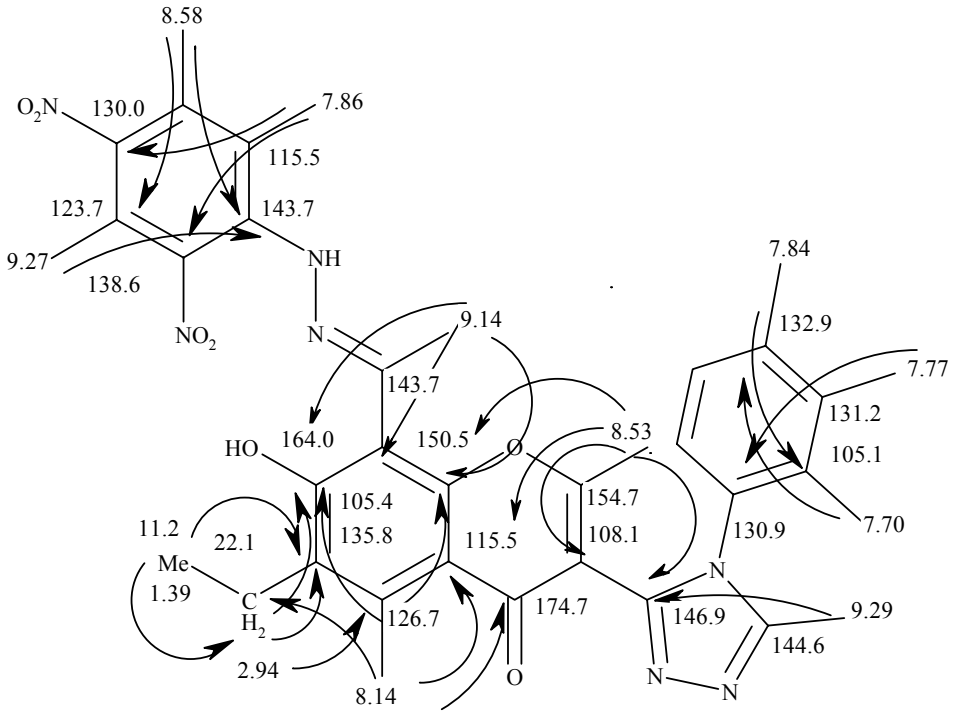



Fig. 1. Assignment of the signals in the $^{1}$H NMR spectra of hydrazone **4b**. The arrows indicate the most important HMBC correlations, serving as the basis for assignment of the quaternary carbon atoms. The chemical shifts of the protons and carbon atoms are given next to the corresponding atoms.

The hydrolysis of imines **5** in a mixture of hydrochloric and acetic acids leads to the formation of 9-azolyl-3-(4-phenyl-4H-1,2,4-triazol-3-yl)pyrano[2,3-*f*]chromene-3,4-diones **6**. Both imino derivatives **5** and α-pyrono[2,3-*f*]chromene-4,8-diones **6** are high-melting compounds with blue fluorescence in UV light.

The composition and structure of imines **5** and diones **6** were supported by elemental analysis as well as IR and NMR spectroscopy (Tables 1 and 2). The IR spectra of α-pyrono[2,3-*f*]chromones **6** show a strong band for the C=O stretching vibrations of the chromone carbonyl group, which is also characteristic for imines **5** as well as an additional strong band for the lactone carbonyl at 1720-1730 cm$^{-1}$, which corresponds to previous results [2, 11, 13]. The $^{1}$H NMR spectra of diones **6** taken in $CF_3CO_2D$ show the same set of characteristic signals for the protons of the chromone, triazole, and azaheterocyclic parts of the molecular as for imino derivatives **5** but the singlets of the protons at lowest field H-10 are shifted downfield by 0.2-0.3 ppm. Analysis of the $^{13}$C NMR DEPT spectrum as well as HMQC and HMBC heteronuclear correlation spectra was used to

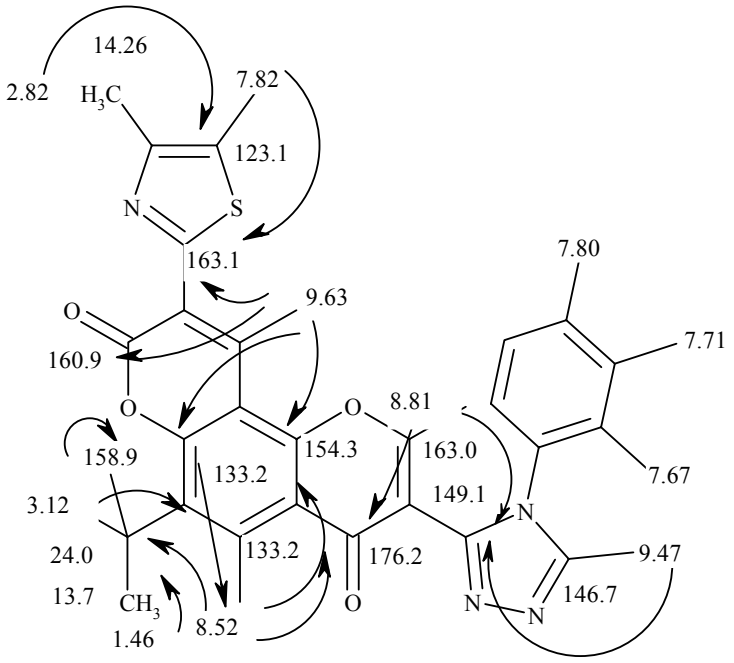



Fig. 2. Assignment of the signals in the $^{13}C$ NMR spectrum of dione **6a**. The most important correlations found in the HMBC spectrum are shown by arrows. The chemical shifts of the protons and carbon atoms are given near the corresponding atoms.

TABLE 1. Characteristics of the Compounds Synthesized **1, 4-6**

| Compound | Empirical formula | Found, % / Calculated, % | | mp, °C | Yield, % |
|---|---|---|---|---|---|
| | | N | S | | |
| **1** | $C_{20}H_{15}N_3O_4$ | 11.68 / 11.63 | — | 243 | –* |
| **4a** | $C_{26}H_{21}N_5O_3$ | 15.53 / 15.51 | — | 278 | 62 |
| **4b** | $C_{26}H_{19}N_7O_7$ | 18.00 / 18.11 | — | > 300 | 74 |
| **5a** | $C_{26}H_{19}N_5O_3S$ | 14.67 / 14.55 | 6.49 / 6.66 | 265 | 46 |
| **5b** | $C_{31}H_{20}BrN_5O_3S$ | 11.18 / 11.25 | 5.27 / 5.15 | > 300 | 75 |
| **5c** | $C_{29}H_{19}N_5O_3S$ | 13.63 / 13.53 | 6.06 / 6.20 | 181 | 58 |
| **5d** | $C_{30}H_{20}N_6O_3S$ | 15.53 / 15.43 | 5.77 / 5.89 | > 300 | 57 |
| **5e** | $C_{30}H_{22}N_6O_3$ | 16.31 / 16.33 | — | 275 | 41 |
| **6a** | $C_{26}H_{18}N_4O_4S$ | 11.60 / 11.61 | 6.53 / 6.65 | 279 | 86 |
| **6b** | $C_{31}H_{19}BrN_4O_4S$ | 8.87 / 8.99 | 5.28 / 5.14 | > 300 | 67 |
| **6c** | $C_{29}H_{18}N_4O_4S$ | 10.72 / 10.81 | 6.10 / 6.18 | > 300 | 65 |
| **6d** | $C_{30}H_{19}N_5O_4S$ | 12.74 / 12.84 | 5.72 / 5.88 | > 300 | 64 |

* Yield of compounds **1** 46% (method A) and 36% (method B).

confirm the structure of dione **6a** as in the case of hydrazone **4b**. As expected, the DEPT spectrum with complete multiplicity editing shows signals for one methylene group, two methyl groups, and eight nonequivalent aromatic CH fragments (two of which have double intensity).

Thus, the reaction of 6-ethyl-8-formyl-7-hydroxy-3-(4-phenyl-4H-1,2,4-triazol-3-yl)chromone (**1**) with 2-azolylacetonitriles under mild conditions gives previously unreported 8-iminopyrano[2,3-*f*]chromen-4-ones, whose acid hydrolysis leads to pyrano[2,3-*f*]chromene-4,8-diones containing azaheterocyclic substituents at C-3 and C-9.

TABLE 2. $^1$H NMR Spectra of Products **1, 4-6**

| Com-pound | Chemical shifts, δ, ppm (SSCS, *J*, Hz)* |
|---|---|
| **1** | 1.21 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 2.67 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.42 (5H, s, C$_6$H$_5$); 7.91 (1H, s, H-5); 8.74 (1H, s, H-2); 8.81 (1H, s, H-5' Tr);*$^2$ 10.54 (1H, s, CHO); 12.82 (1H, s, OH) |
| **4a** | 1.40 (3H, t, *J* = 7.2, 6-C<u>H</u>$_3$CH$_2$); 2.93 (2H, q, *J* = 7.2, 6-CH$_3$C<u>H</u>$_2$); 7.62 (5H, s, NHC$_6$<u>H</u>$_5$); 7.69 (2H, d, *J* = 7.6, H-2",6" Ph); 7.78 (2H, t, *J* = 7.6, H-3",5" Ph); 7.86 (1H, t, *J* = 7.6, H-4" Ph); 8.22 (1H, s, H-5); 8.53 (1H, s, H-2); 9.32 (1H, s, 8-CH); 9.34 (1H, s, H-5' Tr) |
| **4b** | 1.39 (3H, t, *J* = 7.2, 6-C<u>H</u>$_3$CH$_2$); 2.94 (2H, q, *J* = 7.2, 6-CH$_3$C<u>H</u>$_2$); 7.70 (2H, d, *J* = 8.0, H-2",6" Ph); 7.77 (2H, t, *J* = 8.0, H-3",5" Ph); 7.84 (1H, t, *J* = 8.0, H-4" Ph); 7.86 (1H, d, *J* = 9.2, H-6'''); 8.14 (1H, s, H-5); 8.53 (1H, s, H-2); 8.58 (1H, dd, $J_{5''',6'''}$ = 9.2, $J_{5''',3'''}$ = 2.0, H-5'''); 9.14 (1H, s, 8-CH); 9.27 (1H, d, *J* = 2.0, H-3'''); 9.29 (1H, s, H-5' Tr) |
| **5a** | 1.43 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 2.66 (3H, s, CH$_3$-4‴ Th); 3.13 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.55 (1H, s, H-5‴ Th); 7.61 (2H, d, *J* = 7.6, H-2",6" Ph); 7.66 (2H, t, *J* = 7.6, H-3",5" Ph); 7.73 (1H, t, *J* = 7.6, H-4" Ph); 8.53 (1H, s, H-5); 8.80 (1H, s, H-2); 9.21 (1H, s, H-5' Tr); 9.47 (1H, s, H-10) |
| **5b** | 1.58 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 3.27 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.75-7.87 (9H, m, C$_6$H$_5$, *p*-BrC$_6$H$_4$); 8.06 (1H, s, H-5‴ Th); 8.66 (1H, s, H-5); 8.98 (1H, s, H-2); 9.41 (1H, s, H-5' Tr); 9.60 (1H, s, H-10) |
| **5c** | 1.49 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 3.19 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.65-7.77 (5H, m, C$_6$H$_5$); 7.97-8.04 (2H, m, H-5'",6'" Bt); 8.23 (1H, d, *J* = 8.0, H-7'" Bt); 8.29 (1H, d, *J* = 8.0, H-4'" Bt); 8.58 (1H, s, H-5); 8.91 (1H, s, H-2); 9.37 (1H, s, H-5' Tr); 9.52 (1H, s, H-10) |
| **5d** | 1.57 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 3.52 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.73-8.17 (10H, m, 2C$_6$H$_5$); 8.46 (1H, s, H-5); 8.88 (1H, s, H-2); 9.39 (1H, s, H-5' Tr); 9.66 (1H, s, H-10) |
| **5e** | 1.49 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 3.19 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 4.30 (3H, s, N–CH$_3$); 7.62-7.77 (5H, m, C$_6$H$_5$); 7.92–7.99 (4H, m, H-4",5",6",7"); 8.73 (1H, s, H-5); 8.76 (1H, s, H-2); 9.50 (1H, s, H-5' Tr); 9.54 (1H, s, H-10) |
| **6a** | 1.46 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 2.82 (3H, s, CH$_3$-4‴ Th); 3.12 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.67 (2H, d, *J* = 8.0, H-2",6" Ph); 7.71 (2H, t, *J* = 8.0, H-3",5" Ph); 7.80 (1H, t, *J* = 8.0, H-4" Ph); 7.82 (1H, s, H-5‴ Th); 8.52 (1H, s, H-5); 8.81 (1H, s, H-2); 9.47 (1H, s, H-5' Tr); 9.63 (1H, s, H-10) |
| **6b** | 1.48 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 3.21 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.66-7.84 (9H, m, C$_6$H$_5$, *p*-BrC$_6$H$_4$); 8.27 (1H, s, H-5‴ Th); 8.55 (1H, s, H-5); 8.82 (1H, s, H-2); 9.42 (1H, s, H-5' Tr); 9.86 (1H, s, H-10) |
| **6c** | 1.48 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 3.16 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.67 (2H, d, *J* = 7.6, H-2",6" Ph); 7.72 (2H, t, *J* = 7.6, H-3",5" Ph); 7.80 (1H, t, *J* = 7.6, H-4" Ph); 7.96 (1H, t, *J* = 8.0, H-6'" Bt); 8.04 (1H, t, *J* = 8.0, H-5'" Bt); 8.32 (1H, d, *J* = 8.0, H-7'" Bt); 8.37 (1H, d, *J* = 8.0, H-4'" Bt); 8.58 (1H, s, H-5); 8.85 (1H, s, H-2); 9.46 (1H, s, H-5' Tr); 9.83 (1H, s, H-10) |
| **6d** | 1.44 (3H, t, *J* = 7.6, 6-C<u>H</u>$_3$CH$_2$); 3.12 (2H, q, *J* = 7.6, 6-CH$_3$C<u>H</u>$_2$); 7.62-8.16 (10H, m, 2C$_6$H$_5$); 8.50 (1H, s, H-5); 8.77 (1H, s, H-2); 9.43 (1H, s, H-5' Tr); 9.74 (1H, s, H-10) |

* The spectra were taken in DMSO-d$_6$ (chromone **1**) and CF$_3$CO$_2$D (**4-6**).

*$^2$ Bt – benzothiazole, Th = thiazole, Tr = triazole.

## EXPERIMENTAL

The $^{1}H$ NMR spectra were taken on a Varian Mercury 400 spectrometer at 400 MHz with TMS as the internal standard. The $^{13}C$ NMR, DEPT, HMQC, and HMBC spectra were taken in $CF_3CO_2D$. The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The purity of the products was monitored by thin-layer chromatography on Silufol UV-254 plates using 9:1 chloroform–methanol as the eluent.

**6-Ethyl-8-formyl-7-hydroxy-3-(4-phenyl-4H-1,2,4-triazol-3-yl)chromone (1).** A. A solution of chromone **2** [14] (3.33 g, 10 mmol) and hexamethylenetetramine (8.41 g, 60 mmol) in glacial acetic acid (30 ml) was heated on a steam bath for 8 h, poured into 30 ml of a 1:2 mixture of concentrated hydrochloric acid and water heated at reflux, and diluted by adding 40 ml water. After several hours, the precipitate formed was filtered off and recrystallized from ethanol to give 1.66 g chromone **1**.

B. A solution of chromone **3** [15] (0.42 g, 1 mmol) and hexamethyltetramine (0.25 g, 1.8 mmol) was heated in acetic acid (2.5 ml) at reflux for 1 h, poured into a mixture of ice and 4 ml hydrochloric acid, and diluted by adding 10 ml water. After 12 h, the precipitate formed was filtered off to give 0.13 g chromone **1**.

**Arylhydrazones of 6-Ethyl-8-formyl-7-hydroxy-3-(4-phenyl-4H-1,2,4-triazol-3-yl)chromone 4a,b.** The aryl hydrazine (0.5 mmol) was added to a solution of chromone **1** (0.18 g, 0.5 mmol) in ethanol (10 ml), heated at reflux for 30 min. After cooling, the precipitate was filtered off. The products were recrystallized from DMF.

**9-Azolyl-6-ethyl-8-imino-3-(4-phenyl-4H-1,2,4-triazol-3-yl)pyrano[2,3-*f*]chromen-4-ones 5a-e.** Corresponding 9-azolylacetonitrile (1 mmol) and three drops of piperidine were added to a solution of chromone **1** (0.36 g, 1 mmol) in 2-propanol (35 ml) and maintained at room temperature for 12 h. The precipitate formed was filtered off and washed with 2-propanol.

**9-Azolyl-6-ethyl-3-(4-phenyl-4H-1,2,4-triazol-3-yl)pyrano[2,3-*f*]chromen-4,8-diones 6a-d.** The corresponding 9-azolyl-6-ethyl-8-imino-3-(4-phenyl-4H-1,2,4-triazol-3-yl)pyrano[2,3-*f*]chromen-4-one **5** (1 mmol) in a mixture acetic acid (5 ml) and hydrochloric acid (1 ml) was heated at reflux for 10 min. After cooling, the precipitate formed was filtered off, washed with water, and recrystallized from DMF.

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