A New Site-Selective Route For Synthesis of Functionalized Imidazo[2,1-*c*][1,2,4]Triazoles

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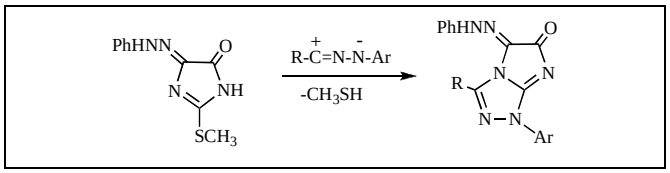
Received January 29, 2006



Reactions of 4-arylhydrazono-2-methylthio-imidazolin-5(1*H*)-one **3** with various hydrazonoyl halides **1** proved to be site-selective and yielded the respective imidazo[2,1-*c*][1,2,4]triazole derivatives **8**. The structure of the latter was elucidated by X-ray analysis and the mechanism of the studied reactions was discussed.

J. Heterocyclic Chem., **44**, 285 (2007).

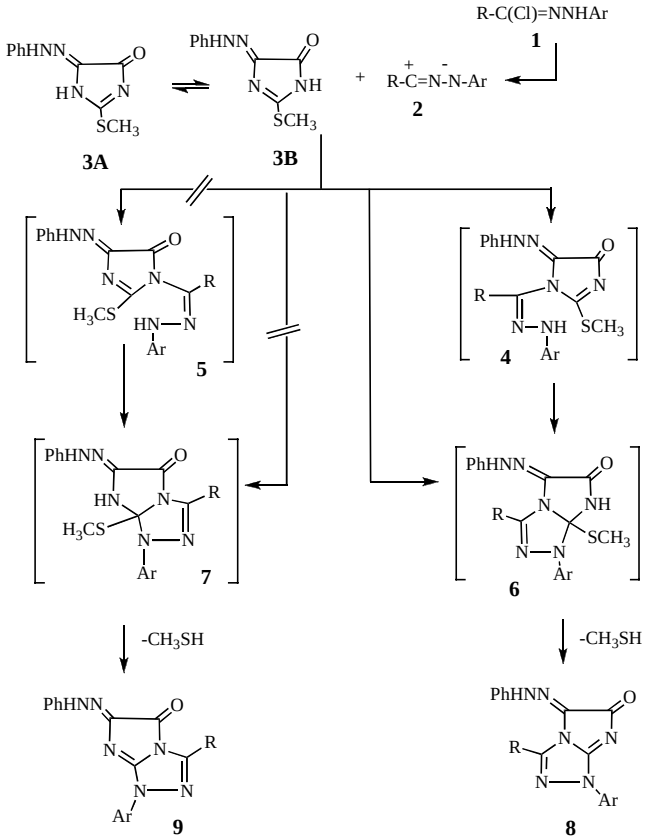
INTRODUCTION

In our laboratory there has been a long standing interest for the utility of nitrilimines **2**, derived from hydrazonoyl halides **1**, in the synthesis of heterocycles and their annelated analogues [1-6]. In this regard, the utilization of the 1,3-dipolar cycloaddition reactions of **2** represents one of the most attractive routes. We wish to report herein a new synthetic strategy for the synthesis of functonalized derivatives of imidazo[2,1-*c*][1,2,4]triazoles **8** based on the intermolecular cycloaddition of nitrilimines **2** to the C=N double bond of 2-methylthioimidazolines **3**. To our knowledge, the various methods reported hitherto for the preparation of imidazo[2,1-*c*][1,2,4]triazoles were based on tandem condensation and cyclization of the appropriate derivatives of either 2-hydrazinoimidazole [7-11] or 3-amino-1,2,4-triazole [12-15].

In addition to our aim to develop a new synthetic route for the title compounds, we planned this work to shed light on the site-selectivity of the reactions to be studied. This is because the 2-methylthio-imidazole derivative **3**, to be used as precursor for the title compounds, can have two possible C=N sites as it can exist in two tautomeric forms [16] (Scheme 1). Although cycloaddition of nitrilimines to acyclic as well as cyclic C=N double bonds have been reported [1-6], to our knowledge, site-selectivity in the cycloaddition of nitrilimines to systems possessing two or more different C=N dipolarophilic sites as in **3** has not been investigated. Herein, we report the remarkable site-selectivity observed in the cycloaddition of nitrilimines **2** to **3**.

Furthermore, our interest in synthesis of the title compounds is due to the fact that many imidazo[2,1-*c*]-[1,2,4]triazole derivatives were reported as antifungal drugs [7], hair dye couplers [17] and photographic materials [18].

Scheme 1



Ar = XC_6H_4 : R / X : a, Ph / H; b, Ac / H; c, Ac / 3-Me; d, Ac / 4-Me; e, Ac / 4-MeO; f, Ac / 3-Cl; g, Ac / 4-Cl; h, Ac / 3-NO_2; i, EtOCO / H; j, EtOCO / 4-Me; k, EtOCO / 4-Cl; l, EtOCO / 4-NO_2

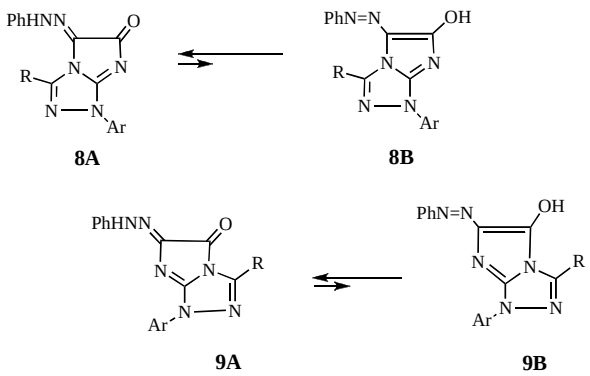
RESULTS AND DISCUSSION

The required reagents namely the hydrazonoyl halides **1** [19-21] and 2-methylthio-4-phenylhydrazono-imidazolin-

5(1*H*)-one **3** [22] were prepared as previously reported. When equimolar quantities of **3** and each of the hydrazonoyl halides **1** in ethanol in the presence of sodium ethoxide were stirred at room temperature for 15 h, a single product was obtained in each case as evidenced by TLC analysis of the crude product. The elemental analyses and spectral (MS, IR, and ^{1}H NMR) data of the products isolated are given in the Experimental section. All data were in full agreement with either of the two isomeric structures **8** and **9** (Scheme 1).

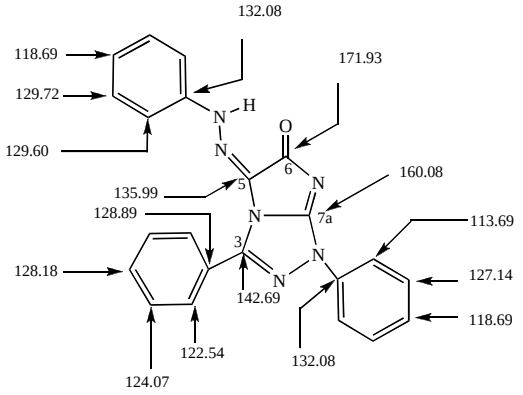
Next, the tautomerism of the isolated products was examined. As shown in Chart 1, each of the two possible isomeric structures **8** and **9** can have two possible tautomeric forms namely the keto-hydrazone A and the hydroxy-azo B forms. Of these forms, structure A seems to be the form of choice as it is consistent with their electronic absorption and ^{1}H NMR spectra. For example, like typical hydrazones [23,24], the electronic absorption spectra of the products isolated in dioxane revealed in each case two characteristic absorption bands in the regions 410 - 399 and 301 - 287 nm (Table 1). The spectra of the unsubstituted derivative **8a** isolated from reaction of **1a** with **3**, taken as representative example of the series prepared, in different solvents exhibited little if any solvent dependence (Table 1). On the basis of such absorption patterns, it can be concluded that the studied compounds have in solution one tautomeric form namely the keto-hydrazone tautomer A (Chart 1). This conclusion was also confirmed by the ^{1}H and ^{13}C NMR spectra of the studied compounds. Thus, whereas the ^{1}H NMR spectra showed hydrogen bonded hydrazone NH proton signal in the region δ 11.00 – 12.00 (see Experimental) [25,26], they revealed the absence of signals at δ 12.0 – 16.0 which are characteristic for the OH proton of the hydroxy-azo compounds [27]. Also, the signals that appeared in the ^{13}C NMR spectrum of compound **8a**, taken as a typical example of the series prepared are shown together with assignments in Chart 2.

Chart 1



The foregoing spectral data cannot, however, distinguish between the two possible isomeric structures

Chart 2



8A and **9A** (Scheme 1). To identify the actual structure of the products isolated from the studied reactions, we have turned to X-ray crystallographic analysis. The ORTEP drawing of the product isolated from reaction of **1i** with **3**, taken as a representative example of the series prepared, is shown in Figure 1 with selected bond distances and bond angles depicted in Table 2 [28]. This ORTEP indicates that the structure of the products isolated from the studied reactions of **1** with **3** is **8A** and not **9A**. This finding indicates that the studied reactions of **1** with **3** are site-selective and proceed *via* intermediates of type **6** (Scheme 1). The latter intermediate can result through

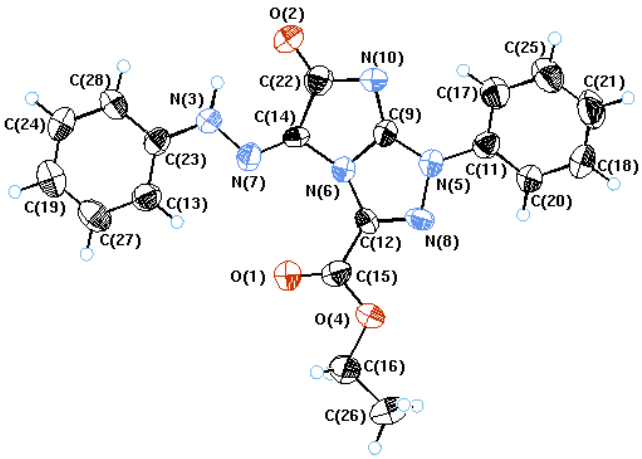


Figure 1. ORTEP plot of the molecular structure of compound **8i**. The crystallographic numbering does not reflect the systematic numbering. Selected bond distances and bond angles are shown in Table

initial 1,3-addition of **3** to the nitrilimine **2**, generated *in situ* from the halide **1**, to give the respective amidrazone **4** which in turn cyclizes to give **6** (Scheme 1). Alternatively, the nitrilimines **2** may cycloadd to **3** to give **6** directly. Elimination of methanethiol from the latter cycloadduct **6** gives **8** as end the product. Attempts to isolate either of

the intermediates **4** or **6** failed, however. This suggests that such intermediates are consumed *in situ* as soon as they are formed to give **8** as end products (Scheme 1).

In conclusion, under the reaction conditions chosen, the studied reactions of **1** with **3** are site-selective and provide a new route for synthesis of the title compounds **8** exclusively from easily accessible starting materials.

Table 1

Electronic Absorption Spectra of Compounds **8** in Dioxane

Cpd. No.	λ_{max} (log ε)
8a[a]	387 (3.45), 287 (3.62)
8b	403 (3.59), 288 (4.10)
8c	406 (3.48), 287 (4.10)
8d	406 (3.68), 301 (3.69)
8e	405 (3.44), 287 (3.80)
8f	406 (3.65), 287 (4.40)
8g	404 (3.56), 286 (3.80)
8h	410 (3.60), 287 (4.57)
8i	399 (3.57), 287 (4.10)
8j	399 (3.69), 287 (4.40)
8k	403 (3.63), 286 (4.10)
8l	403 (3.56), 287 (4.10)

[a] Solvent, λ_{max} (log ε): EtOH: 390 (3.87), 271(3.92); Chloroform: 397 (3.93), 266 (3.95); Acetic acid: 393 (3.99), 260 (4.03); Hexane: 386 (4.32), 289 (3.29); Pyridine: 394 (4.31), 301 (4.33).

Table 2

Selected Bond Lengths and bond angles in the ORTEP of compound **8i** in the crystal. The crystallographic numbering does not reflect systematic numbering.

Bond length, °A	Bond length, °A	Bond length, °A
N5-N8 (1.395)	N10-C22 (1.368)	C12-C15 (1.476)
N8-C12 (1.312)	C22-O2 (1.248)	C15-O1 (1.208)
C12-N6 (1.379)	C22-C14 (1.492)	C15-O4 (1.328)
N6-C9 (1.363)	C14-N6 (1.423)	O4-C16 (1.458)
C9-N5 (1.350)	C14-N7 (1.274)	C16-C26 (1.484)
N5-C11 (1.434)	N7-N3 (1.331)	
C9-N10 (1.328)	N3-C23 (1.392)	

Angle (ω)	Angle (ω)	Angle (ω)
C9-N5-C11 (129.4)	C12-N6-C14 (148.0)	N6-C14-N7 (123.9)
N8-N5-C11 (119.6)	C14-N6-C12 (148.0)	N7-C14-C22 (134.3)
N8-N5-C9 (111.0)	N5-C9-N6 (106.2)	C14-N7-N3 (116.6)
N5-N8-C12 (104.1)	N6-C9-N10 (118.6)	N7-N3-C23 (117.7)
N8-C12-N6 (112.0)	N10-C9-N5 (135.1)	O1-C15-O4 (126.2)
N8-C12-C15 (122.8)	C9-N10-C22 (101.7)	O1-C15-C12 (123.2)
N6-C12-C15 (125.2)	C14-C22-O2 (121.6)	C12-C15-O4 (110.6)
C12-N6-C9 (106.6)	N10-C22-O2 (125.7)	C15-O4-C16 (116.1)
C9-N6-C14 (105.2)	O2-C22-C14 (121.6)	O4-C16-C26 (107.9)

EXPERIMENTAL

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) in DMSO-d_6 and the chemical shifts were related to that of the solvent. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Electronic absorption spectra were recorded on Perkin- Elmer Lambada 40 spectrophotometer. Single-crystal X-ray diffraction analysis was recorded using Bruker nonius draft macscience**.** Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. The starting hydrazonoyl halides **1** [19-21] and 2-methylthio-4-phenylhydrazonoimidazolin-5(1*H*)-one **3** [22] were all prepared according to literature methods.

1-Aryl-5-phenylhydrazono-3-substituted-1*H*-imidazo-[2,1-*c*]-[1,2,4]triazol-6(5*H*)-ones (8a-l). General Procedure. To an ethanolic sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmole) and absolute ethanol (20 ml)] was added a mixture of 2-methylthio-4-phenylhydrazonoimidazolin-5(1*H*)-one **3** (2.34 g, 10 mmole) and the appropriate hydrazonoyl halide **1** (10 mmole). The reaction mixture was stirred overnight (15 hr.) at room temperature. During this time, all methanethiol evolved and a precipitate was formed. The solid formed was collected by filtration, washed with ethanol and crystallized from the appropriate solvent to give **8**. The physical constants together with the spectral data of compounds **8a-l** are listed as follows.

1,3-Diphenyl-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]-triazol-6(5*H*)-one (8a). This compound was obtained as yellow solid (AcOH), (2.66 g, 70 %), m.p. 222°C, ir: 3198 (NH), 1690 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 7.06-8.47 (m, 15H, ArH)), 12.19 (s, 1H, NH), ^{13}C nmr (DMSO-d_6) δ 113.69, 118.69, 122.54, 124.07, 127.14, 128.18, 128.89, 129.60, 129.72, 132.08, 135.99, 142.69, 160.08, 171.93; ms: m/z (%) 381 (M^++1, 22), 380 (M^+, 100), 288 (78), 262 (35), 194 (14), 117 (28), 91 (55), 77 (31). *Anal.* Calcd. for $C_{22}H_{16}N_6O$: C, 69.46; H, 4.24; N, 22.09. Found: 69.63; H, 4.40; N, 22.35

3-Acetyl-1-phenyl-5-phenylhydrazono-1*H*-imidazo[2,1-*c*]-[1,2,4]triazol-6(5*H*)-one (8b). This compound was obtained as yellow solid (AcOH-H_2O) (1.25 g, 36 %), m.p.226°C; ir: 3198 (NH), 1701, 1697 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 2.79 (s, 3H, CH_3), 7.06-8.16 (m, 10H, ArH), 12.17 (s,1H, NH); ms: m/z (%) 348 (M^++2, 4), 347 (M^++1, 32), 346 (M^+, 46), 254 (24), 229 (96), 212 (43), 145 (31), 118 (34), 91 (70), 77 (100). *Anal.* Calcd. for $C_{18}H_{14}N_6O_2$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.24; H, 4.24; N, 24.30.

3-Acetyl-1-(3-methylphenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]-triazol-6(5*H*)-one (8c). This compound was obtained as orange solid (AcOH) (0.94 g, 26 %), m.p. 240°C; ir: 3200(NH), 1700, 1693 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 2.36 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 6.99-8.00 (m, 9H, ArH), 11.99 (s,1H, NH); ms: m/z (%) 362 (M^++2, 4), 361 (M^++1, 20), 360 (M^+, 73), 268 (29), 243 (100), 226 (31), 201 (10), 159 (21), 91 (77), 77 (31). *Anal.* Calcd. for $C_{19}H_{16}N_6O_2$: C, 63.33; H, 4.48; N, 23.30. Found: C, 63.08; H, 4.40; N, 23.26.

3-Acetyl-1-(4-methylphenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]-triazol-6(5*H*)-one (8d). This compound was obtained as yellow solid (AcOH); (1.08g, 30 %), m.p. 254°C, ir: 3209 (NH), 1701, 1600 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 7.06 (d, J = 8Hz, 2H), 7.10-7.78 (m, 5H, ArH), 8.01 (d, J = 8 Hz, 2H), 12.14 (s, 1H, NH); ms: m/z (%) 362 (M^++2, 5), 361 (M^++1, 36), 360 (M^+, 100), 243 (76), 226 (25), 159 (11), 91 (23), 77 (8). *Anal.* Calcd. for $C_{19}H_{16}N_6O_2$: C, 63.33; H, 4.48 ; N, 23.30. Found: C, 63.29; H, 4.39; N, 23.52.

3-Acetyl-1-(4-methoxyphenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]triazol-6-(5*H*)-one (8e). This compound was obtained as yellow solid (AcOH), (0.97 g, 21 %), m.p.250°C; ir: 3229 (NH), 1697, 1562 (CO) cm^{-1}; ^{1}H nmr

(DMSO-d_6) δ 2.72 (s, 3H, CH_3), 2.85 (s, 3H, OCH_3), 7.05 (d, J = 8Hz, 2H), 7.10-7.80 (m, 5H, ArH), 7.98 (d, J = 8 Hz, 2H), 12.00 (s, 1H, NH); ms: m/z (%) 377 (M^++1, 25), 376 (M^+, 90), 284 (29), 259 (100), 242 (29), 175 (23), 147 (27), 121 (19), 91 (32), 77 (28). *Anal*. Calcd. for $C_{19}H_{16}N_6O_3$: C, 60.63; H, 4.28; N, 22.33. Found: C, 60.91; H, 4.24 ; N, 22.25.

3-Acetyl-1-(3-chlorophenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]-triazol-6(5*H*)-one (8f). This compound was obtained as orange solid (AcOH) (0.88 g, 23 %), m.p.248°C; ir: 3206, (NH), 1705, 1630 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.73 (s, 3H, CH_3), 7.00-7.88 (m, 9H, ArH), 11.95 (s, 1H, NH); ms: m/z (%) 383 (M^++2, 6), 382 (M^++1, 24), 381 (M^+, 25), 337 (11), 263 (100), 222 (3), 221 (15), 179 (22), 125 (13), 91 (78), 77 (40). *Anal*. Calcd. for $C_{18}H_{13}ClN_6O_2$: C, 56.78; H, 3.44; N, 22.07. Found : C,56.47; H,3.73; N, 22.06.

3-Acetyl-1-(4-chlorophenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]-triazol-6(5*H*)-one (8g). This compound was obtained as yellow solid (AcOH) (1.18 g, 31 %), m.p. 220°C; ir: 3213 (NH), 1705, 1600 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.78 (s, 3H, CH_3), 7.00 (d, J = 8Hz, 2H), 7.05-7.90 (m, 5H, ArH), 8.05 (d, J = 8 Hz, 2H), 12.17 (s, 1H, NH); ms: m/z (%) 383 (M^++2, 9), 382 (M^++1, 37), 381 (M^+, 33), 337 (8), 288 (24), 263 (100), 118 (35), 91 (63), 77 (33). *Anal*. Calcd. for $C_{18}H_{13}ClN_6O_2$: C, 56.78; H, 3.44; N, 22.07. Found: C, 56.59; H, 3.55; N, 22.15.

3-Acetyl-1-(3-nitrophenyl)-5-phenylhydrazono-1*H*-imidazo-[2,1-*c*][1,2,4]-triazol-6(5*H*)-one (8h). This compound was obtained as brown solid (AcOH) (0.86 g, 22 %), m.p. 265°C; ir: 3206 (NH), 1705, 1550 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.83 (s, 3H, CH_3), 7.00-7.88 (m, 9H, ArH), 11.98 (s, 1H, NH); ms: m/z (%) 393 (M^++1, 6), 392 (M^+, 24), 274 (100), 190 (14), 144 (12), 118 (48), 91 (88), 77 (41). *Anal*. Calcd. for $C_{18}H_{13}N_7O_4$: C, 55.25; H, 3.35; N, 25.05. Found: C, 55.62; H, 3.73; N, 24.95.

3-Ethoxycarbonyl-1-phenyl-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]-triazol-6(1*H*)-one (8i). This compound was obtained as yellow solid (AcOH) (1.39 g, 37 %), m.p. 232°C; ir: 3190 (NH), 1740, 1697 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.53 (t, J= 7 Hz,3H, CH_3), 4.65 (q, J= 7 Hz, 2H, CH_2), 7.06-8.16 (m, 10H, ArH), 12.24 (s,1H, NH); ms: m/z (%) 379 (M^++2, 10), 377 (M^++1, 45), 376 (M^+, 76), 284 (32), 213 (92), 145 (62), 91(64), 77 (100). *Anal*. Calcd. for $C_{19}H_{16}N_6O_3$ (376.38): C, 60.63; H, 4.28; N, 22.33. Found: C, 60.60; H, 4.20; N, 22.35.

3-Ethoxycarbonyl-1-(4-methylphenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]triazol-6(5*H*)-one (8j). This compound was obtained as yellow solid (AcOH) (1.4 g, 36 %), m.p. 238°C; ir: 3332 (NH), 1724, 1643 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.65 (t, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.62 (q, 2H, CH_2), 7.07-8.02 (m, 9H, ArH), 12.22 (s, 1H, NH); ms: m/z (%) 390 (M^+, 30), 376 (49), 298 (11), 284 (33), 273 (13), 259 (27), 227 (73), 159 (34), 131 (27), 118 (30), 105 (45), 91 (100), 77(46). *Anal*. Calcd. for $C_{20}H_{18}N_6O_3$: C, 61.53; H, 4.65; N, 21.53. Found: C, 61.39; H, 5.45; N, 21.40.

3-Ethoxycarbonyl-1-(4-chlorophenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4]triazol-6(5*H*)-one (8k). This compound was obtained as yellow solid (AcOH) (1.44 g, 35 %), m.p. 242°C, ir: 3213 (NH), 1701, 1655 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.56 (t, 3H, CH_3), 4.62 (q, 2H, CH_2), 7.08-8.13 (m, 9H, ArH), 12.22 (s,1H, NH); ms: m/z (%) 412 (M^++2, 12), 411 (M^++1, 8), 410 (M^+, 26), 396 (38), 304 (28), 279 (27), 247 (68), 179 (22), 151 (37), 127 (20), 111 (50), 91 (100), 77 (63). *Anal*. Calcd. for $C_{19}H_{15}ClN_6O_3$: C, 55.55; H, 3.68; N, 20.46. Found: C, 55.45; H, 3.58; N, 20.49.

3-Ethoxycarbonyl-1-(4-nitrophenyl)-5-phenylhydrazono-1*H*-imidazo[2,1-*c*][1,2,4] triazol-6(5*H*)-one (8l). This compound was obtained as yellow solid (AcOH) (0.84 g, 20 %), m.p.288°C; ir (KBr) υ 3202 (NH), 1747, 1709 (CO) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.33 (t, 3H, CH_3),4.33(q, 2H, CH_2), 7.30-8.28 (m, 9H, ArH), 10.69 (s,1H, NH); ms: m/z (%) 424 (M^++2, 2), 423 (M^++1, 5), 422 (M^+, 24), 348 (13), 304 (41), 258 (78), 187(20), 144 (17), 118 (48), 91 (100), 77 (44). *Anal*. Calcd. for $C_{19}H_{15}N_7O_5$: C, 54.16; H, 3.59; N, 23.27. Found: C, 54.13; H, 3.48; N, 23.15.

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[28] All crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC – 286364. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.