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Catalyst-free, aqueous and highly diastereoselective synthesis of new 5-substituted 1*H*-tetrazoles via a multi-component domino Knoevenagel condensation/1,3 dipolar cycloaddition reaction

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ABSTRACT

An approach for the synthesis of new 5-substituted-tetrazoles via multi-component domino Knoevenagel condensation/1,3 dipolar cycloaddition reaction of carbonyl compounds, malononitrile and sodium azide in water without assistance of any catalyst has been reported. This general protocol provides a wide variety of 5-substituted 1*H*-tetrazoles in good yields under mild reaction conditions.

1. Introduction

Nowadays, the main goals of 'green chemistry' are to increase process selectivity, maximize the use of starting materials, and to replace hazardous reagents with eco-friendly materials. Organic reactions in water without using harmful organic solvents have attracted a great deal of interest in both academic and industrial research because, in addition to environmental concerns, there are beneficial effects of aqueous solvents on rates and selectivities of important organic transformations.[1]

Multi-component domino reactions (MDR), which can occur in aqueous media have been extensively pursued in the past decade due to their efficient atom economy and green characteristics.[2] These reactions enable multi-step synthesis to be conducted in a one-pot operation to obtain a variety of invaluable products. These processes can avoid time-consuming and costly syntheses involving multistep reactions, protection–deprotection steps, tedious workup and purifications. In addition, these reactions often give excellent chemo- and regioselectivities.[2,3]

The chemistry of heterocycles has acquired immense importance in recent years. The tetrazole function is metabolically stable and a close similarity between the acidic character of the tetrazole group and carboxylic acid group have inspired medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents. 5-Substituted-tetrazoles are reported to possess antibacterial,[4] antifungal,[5] antiviral,[6] analgesic,[7] anti inflammatory,[8] antiulcer[9] and antihypertensive[10] activities. Also, this functional group has roles in coordination chemistry as a ligand, and in various materials science applications including propellants[11] and explosives.[12] Furthermore, tetrazole moieties are important synthons in synthetic organic chemistry.[13] Therefore, a number of methods have been reported for the preparation of tetrazoles.[14,15] One of the major synthetic routes to tetrazole formation is the [2+3] cycloaddition of an organonitrile and an azide salt.[16]

However, many of these protocols have some disadvantages, such as the use of toxic metals, strong Lewis acid, expensive reagents, low yield, drastic reaction conditions, water sensitivity and the presence of hydrazoic acid, which is toxic and explosive. In addition, all of the known methods use organic solvents, in particular, dipolar aprotic solvents, such as DMF.[12,17,18] Recently, Sharpless et al. reported an improved preparation of tetrazoles by the reaction of nitriles and NaN_3 in the presence of Zn(II) salts in water. In the case of sterically hindered aromatic or deactivated alkyl nitriles, high temperature (140–170 °C) and long reaction times are required.[19]

Thus, the development of a convenient and safe process for the preparation of new tetrazole derivatives is an interesting target for investigation. Despite continuous research for the synthesis of tetrazoles and development of new multi-component reactions, only a limited number of multi-component syntheses of tetrazole derivatives have been reported.[15a,20]

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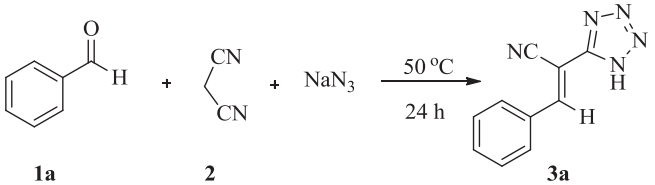
Herein, we would like to report a novel, facile, eco-friendly and one-pot process for synthesis of 5-substituted 1*H*-tetrazoles via a domino Knoevenagel condensation and 1,3 dipolar cycloaddition reaction.

2. Results and discussion

The choice of an appropriate reaction medium is of crucial importance for successful synthesis. Initially, the three-component reaction of benzaldehyde **1a**, malononitrile **2** and sodium azide as a simple model substrate was investigated in different solvents without any catalyst (Table 1). The desired product was scarcely obtained in non-polar solvents (entries 5–7) and even methanol and ethanol as a polar protic solvent failed to produce the desired 1*H*-tetrazole in good yield (entries 8,9). It was found that water is the best solvent with respect to reaction yield (entry 4). This effect can be attributed to the strong hydrogen bond interaction at the organic–water interface, which stabilizes the reaction intermediate.[21] We performed the model reaction using different quantities of reagents in water. The best result was obtained with a 1:1:2 ratio of benzaldehyde, malononitrile and sodium azide.

Table 1
Model reaction, conditions and yield[a]



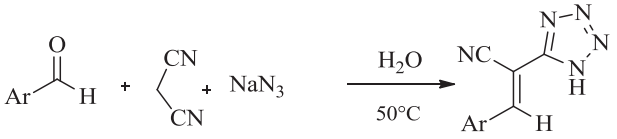
1a **2** **3a**

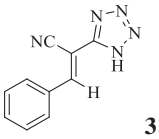
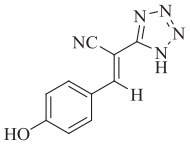
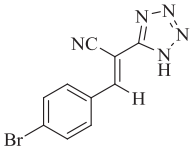
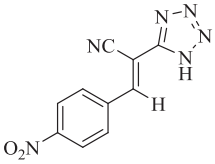
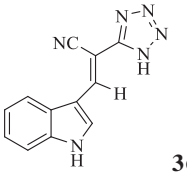
Entry	Solvent	NaN_3 (mmol)	Yield (%)
1	H_2O	1	57
2	H_2O	1.5	75
3	H_2O	2	81
4	H_2O	2.5	82
5	Benzene	2	Trace
6	Toluene	2	Trace
7	$CHCl_3$	2	30
8	MeOH	2	48
9	Ethanol	2	55

[a] Benzaldehyde (1 mmol), malononitrile (1 mmol).

To explore the scope and limitations of the reaction, the procedure was extended to various aromatic aldehydes **1a**–**e**. As indicated in Table 2, the reactions proceeded very efficiently, and led to the formation of the corresponding (*E*)-(1*H*-tetrazole-5-yl) acrylonitrile **3a**–**e** in good yields and stereoselectivities. X-ray crystallographic analysis revealed the relative configuration of the isomer **3b** as depicted in Fig. 1. Details of the structure determination and refinement are described in the Experimental section.

Table 2
Synthesis of tetrazoles **3**



Product	Time (h)	Yield (%)
 **3a**	24	81
 **3b**	24	80
 **3c**	26	63
 **3d**	30	76
 **3e**	24	78

To the best of our knowledge, this new procedure provides the first example of the synthesis of (*E*)-(1*H*-tetrazole-5-yl) acrylonitrile using a three-component domino reaction and this new reaction opens an important field to the use of MCR strategy in 5-substituted 1*H*-tetrazoles synthesis. The reaction preceded very cleanly under mild conditions at 50 °C in the absence of any catalyst. The catalyst-free reactions carried out in water are safe, nontoxic, environmentally friendly and inexpensive. The absence of

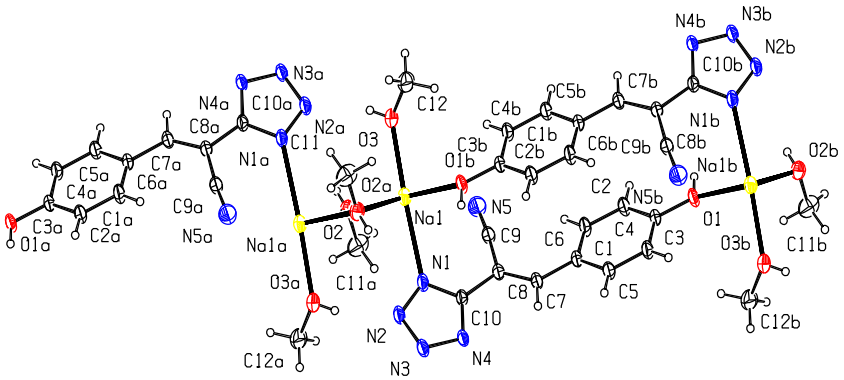
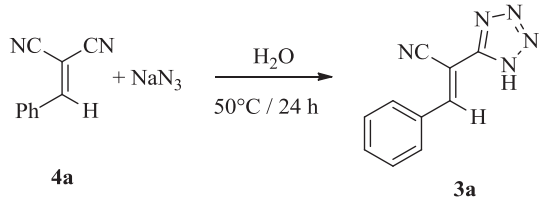


Fig. 1. X-ray crystal structure of sodium salt of **3b**.

catalyst for the reaction avoids the use of moisture-sensitive heavy metals, such as Lewis acids.

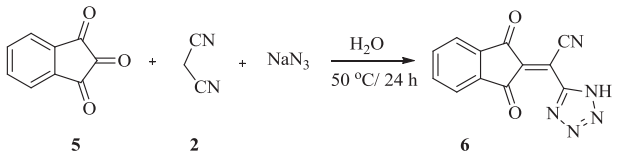
Mechanistically, the formation of tetrazoles **3** can be rationalized by initial formation of arylidenemalononitrile **4** through a Knoevenagel condensation reaction of **1** and **2**. Afterwards the intermediate **4** undergoes [2+3] cycloaddition reaction with the sodium azide to afford product **3**. To clarify the proposed mechanism, first, 2-benzylidenemalononitrile **4a** was synthesized from the condensation of benzaldehyde and malononitrile. Subsequently reaction of **4a** with sodium azide afforded the corresponding (*E*)-3-phenyl-2-(1*H*-tetrazole-5-yl)acrylonitrile **3a** (Scheme 1). Although the role of water as the reaction medium and its mechanism is not clear, this one-pot reaction with regards to the observations of Sharpless et al.,[22] might take place at the interface of organic substrates with water in a heterogeneous system.



4a **3a**

Scheme 1. Reaction of 2-benzylidenemalononitrile and sodium azide.

Encouraged by these results, ninhydrin **5** was selected as an active carbonyl compound and the desired 2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)-2-(1*H*-tetrazole-5-yl)acetonitrile **6** was obtained in 79% yield under the same reaction conditions (Scheme 2).

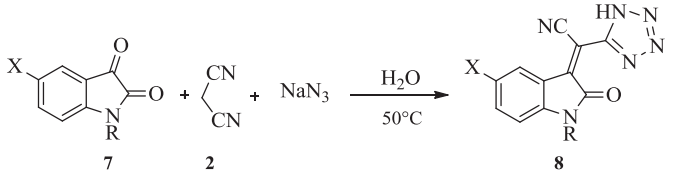


5 **2** **6**

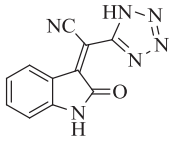
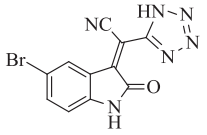
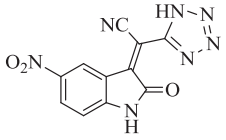
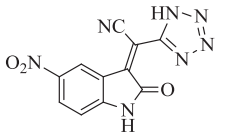
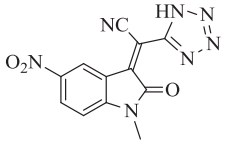
Scheme 2. Synthesis of 2-(1,3-dioxo-1*H*-inden-ylidene)-2-tetrazole-5-yl.

Due to the importance of oxindole derivatives[23,24] and to further explore the potential of this protocol for three-component tetrazoles synthesis, we investigated reaction of isatins **7** instead of aldehyde **1** and obtained the corresponding (*Z*)-oxoindolin-(1*H*-tetrazole-5-yl) acetonitrile **8** in good yields under the same reaction conditions (Table 3). The best evidence for the formation of (*Z*)-configuration is its less steric hindrance and the appearance of a deshielded singlet for 4-H (9.07 ppm, d, $^3J_{HH}$=7.8 Hz,) in the ^{1}H NMR spectrum of **8a** resulting probably from the anisotropic effect of the nitrile group[25] (Supplementary data).

Table 3
Synthesis of oxoindolin-tetrazoles **8**



7 **2** **8**

Product	Time (h)	Yield (%)
 **8a**	24	88
 **8b**	24	67
 **8c**	24	78
 **8d**	30	80
 **8e**	20	79

3. Conclusion

In conclusion, an efficient, green and convenient method for the preparation of new 5-substituted-tetrazoles in water is reported. This new process provides an opportunity to use water and avoid environmentally harmful conventional organic solvents, easy work-up and reduced waste production by the lack of catalyst or additive agent.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. ^{1}H and ^{13}C NMR spectra were obtained on solutions in DMSO-d_6. IR spectra were recorded using a BOMEM MB-Series. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

The chemicals used in this work were obtained from Fluka and Merck and were used without purification.

4.2. General procedure for the synthesis of tetrazoles 3, 6 and 8

A mixture of carbonyl compound (1 mmol), malononitrile (1 mmol) and sodium azide (2 mmol) in H_2O (5 mL) was stirred at 50 °C for appropriate time, after completion of the reaction, as indicated by TLC, the reaction mixture was filtered. To the filtrate was added 30 mL of 2 N HCl with vigorous stirring causing the tetrazole to precipitate. The precipitate was filtered and dried in a drying oven to furnish the tetrazole.

*4.2.1. (E)-3-Phenyl-2-(1H-tetrazole-5-yl) acrylonitrile (**3a**).* Cream powder (0.16 g, yield 81%), mp 168–170 °C. IR (KBr) (ν_{max}/cm^{-1}): 3583, 2130, 1644, 1612, 1498. MS, *m*/*z*: 197 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.67 (br s, NH, overlap with solvent), 7.59 (3H, s, CH–Ar), 8.00 (2H, s, CH–Ar), 8.39 (1H, s, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 97.3, 115.9, 129.7, 130.3, 132.6, 132.8, 148.8, 155.8. Anal. Calcd for $C_{10}H_7N_5$: C, 60.91; H, 3.58; N, 35.51. Found: C, 60.82; H, 3.95; N, 35.44.

*4.2.2. (E)-3-(4-Hydroxyphenyl)-2-(1H-tetrazole-5-yl) acrylonitrile (**3b**).* White powder (0.17 g, yield 80%). Mp 159–161 °C. IR (KBr) (ν_{max}/cm^{-1}): 3425, 3141, 2225, 1600, 1581, 1498. MS, *m*/*z*: 213 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 6.94 (2H, d, $^3J_{HH}$=8.4 Hz, H–Ar), 7.91 (2H, d, $^3J_{HH}$=8.4 Hz, H–Ar), 8.18 (1H, s, CH), 10.63 (1H, br s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 91.8, 116.6, 116.7, 123.7, 133, 148.8, 155.6, 162.2. Anal. Calcd $C_{10}H_7N_5O$: C, 56.34; H, 3.31; N, 32.85. Found: C, 56.28; H, 3.25; N, 32.76. X-ray data for sodium salt of **3b** (suitable crystals for X-ray diffraction analysis were obtained from slow evaporation in MeOH solvent): $C_{10}H_6N_5NaO(2CH_3OH)$, *M*=299.27 g/mol, triclinic system, space group $P\bar{1}$, *a*=8.5926(7), *b*=9.2683(7), *c*=9.2161(7) Å, α=77.105(6), β=82.720(6), γ=80.648(6)°, *V*=702.81(9) Å^3, *Z*=2, *Dc*=1.414 g cm^{-3}, μ(Mo Kα)=0.130 mm^{-1}, crystal dimension of 0.45×0.30×0.15 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL of the X-Step32 suite of programs. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final *R*1=0.0599, *wR*2=0.1853 and *S*=1.004 with 202 parameters using 3766 independent reflection (θ range=2.28–29.15°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **3b** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 837494, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

*4.2.3. (E)-3-(4-Bromophenyl)-2-(1H-tetrazole-5-yl) acrylonitrile (**3c**).* Cream powder (0.17 g, yield 63%). Mp 165–167 °C. IR (KBr) (ν_{max}/cm^{-1}): 3431, 2117, 1530, 1473. MS, *m*/*z*: 274 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.52 (br s, NH, overlap with solvent), 7.68 (2H, d, $^3J_{HH}$=6.3 Hz, H–Ar), 7.81 (2H, d, $^3J_{HH}$=6.3 Hz, H–Ar), 8.02 (1H, s, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 99.6, 117.7, 124, 127.8, 130, 131.4, 132.1, 132.3, 157. Anal. Calcd $C_{10}H_6BrN_5$: C, 43.50; H, 2.19; N, 25.37. Found: C, 43.58; H, 2.14; N, 25.31.

*4.2.4. (E)-3-(4-Nitrophenyl)-2-(1H-tetrazole-5-yl) acrylonitrile (**3d**).* Cream powder (0.18 g, yield 76%). Mp 166–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 3330, 2233, 1602, 1566. MS, *m*/*z*: 242 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.44 (br s, NH, overlap with solvent), 8.12 (2H, d, $^3J_{HH}$=7.4 Hz, H–Ar), 8.29 (2H, d, $^3J_{HH}$=7.4 Hz, H–Ar), 8.32 (1H, s, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 90, 114, 118.4, 124.8, 126.3, 139.1, 146, 146.3. Anal. Calcd $C_{10}H_6N_6O_2$: C, 49.59; H, 2.50; N, 34.70. Found: C, 49.66; H, 2.45; N, 34.78.

*4.2.5. (E)-3-(1H-Indol-3-yl)-2-(1H-tetrazole-5-yl) acrylonitrile (**3e**).* Brown powder (0.18 g, yield 78%). Mp 218–220 °C. IR (KBr) (ν_{max}/cm^{-1}): 3513, 3400, 2218, 1593, 1498. MS, *m*/*z*: 236 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.56 (br s, NH, overlap with solvent), 7.25–7.27 (2H, m, H–Ar), 7.54–7.56 (1H, m, H–Ar), 7.81–7.91 (1H, m, H–Ar), 8.26–8.77 (2H, m, CH), 12.41 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 87, 118.6, 122.1, 123.8, 127.4, 130.5, 136.4, 141.3, 154.4, 154. Anal. Calcd $C_{12}H_8N_6$: C, 61.01; H, 3.41; N, 35.58. Found: C, 61.10; H, 3.449; N, 35.47.

*4.2.6. 2-(1,3-Dioxo-1H-inden-2(3H)-ylidene)-2-(1H-tetrazole-5-yl) acetonitrile (**6**).* Cream powder (0.21 g, yield 81%). Mp 156–158 °C. IR (KBr) (ν_{max}/cm^{-1}): 3311, 2193, 1713, 1612, 1568, 1486. MS, *m*/*z*: 251 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.50 (br s, NH, overlap with solvent), 7.62–7.72 (3H, m, H–Ar), 7.92 (1H, s, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 114.7, 124, 125.3, 133.4, 134.5, 136.2, 137.8, 138.2, 152.1, 162.7, 186.4 (C–Ar and CN). Anal. Calcd for $C_{12}H_5N_5O_2$: C, 57.38; H, 2.01; N, 27.88. Found: C, 57.31; H, 1.97; N, 27.94.

*4.2.7. (Z)-2-(2-Oxoindolin-3-ylidene)-2-(1H-tetrazole-5-yl) acetonitrile (**8a**).* Red powder (0.21 g, yield 88%). Mp 210–212 °C. IR (KBr) (ν_{max}/cm^{-1}): 3406, 3305, 2206, 1720, 1612, 1563, 1467. MS, *m*/*z*: 238 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.38 (br s, NH, overlap with solvent), 6.84 (1H, d, $^3J_{HH}$=7.6 Hz, H–Ar), 6.95 (1H, t, $^3J_{HH}$=7.8 Hz, H–Ar), 7.34 (1H, t, $^3J_{HH}$=7.6 Hz, H–Ar), 9.07 (1H, d, $^3J_{HH}$=7.8 Hz, H–Ar), 10.86 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 110.1, 121.2, 121.7, 128.1, 128.7, 133.1, 133.2, 134.8, 143.4, 151.7, 166.9. Anal. Calcd for $C_{11}H_6N_6O$: 55.46; H, 2.54; N, 35.28. Found: C, 55.55; H, 2.59; N, 35.17.

*4.2.8. (Z)-2-(5-Bromo-2-oxoindolin-3-ylidene)-2-(1H-tetrazole-5-yl) acetonitrile (**8b**).* Brown powder (0.21 g, yield 67%). Mp 218–220 °C. IR (KBr) (ν_{max}/cm^{-1}): 3425, 3147, 2218, 1701, 1574, 1486. MS, *m*/*z*: 317 (M^+), 315 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.37 (br s, NH, overlap with solvent), 6.70–6.72 (1H, m, H–Ar), 7.12–7.19 (1H, m, H–Ar), 7.31 (1H, s, H–Ar), 10.47 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 117.6, 121.4, 124.9, 128.5, 129.1, 130.3, 134.5, 139.3, 149.0, 151.2, 170.5. Anal. Calcd for $C_{11}H_5BrN_6O$: C, 41.66; H, 1.59; N, 26.50. Found: C, 41.58; H, 1.54; N, 26.45.

*4.2.9. (Z)-2-(5-Nitro-2-oxoindolin-3-ylidene)-2-(1H-tetrazole-5-yl) acetonitrile (**8c**).* Dark powder (0.22 g, yield 78%). Mp 225–227 °C. IR (KBr) (ν_{max}/cm^{-1}): 3430, 3171, 2221, 1706, 1566, 1483. MS, *m*/*z*: 283 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.45 (br s, NH, overlap with solvent), 7.16 (1H, d, $^3J_{HH}$=8.6 Hz, H–Ar), 8.10 (1H, d, $^3J_{HH}$=8.6 Hz, H–Ar), 8.76 (1H, s, H–Ar), 10.66 (1H, s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 118.1, 123.8, 124.1, 124.7, 127.6, 128.3, 129.6, 138.3, 149.6, 152.3, 170.1. Anal. Calcd for $C_{11}H_5N_7O_3$: C, 46.65; H, 1.78; N, 34.62. Found: C, 46.73; H, 1.70; N, 34.55.

*4.2.10. (Z)-2-(1-Methyl-2-oxoindolin-3-ylidene)-2-(1H-tetrazole-5-yl) acetonitrile (**8d**).* Brown powder (0.17 g, yield 67%). Mp 214–216 °C. IR (KBr) (ν_{max}/cm^{-1}): 3380, 2212, 1725, 1605, 1466, 1416. MS, *m*/*z*: 252 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.43 (br s, NH, overlap with solvent), 3.20 (3H, s, CH_3). 7.03 (2H, d, $^3J_{HH}$=7.7 Hz, H–Ar), 7.43 (1H, t, $^3J_{HH}$=7.7 Hz, H–Ar), 9.16 (1H, d, $^3J_{HH}$=7.8 Hz, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 26.5, 107.8, 109.1, 116.5, 120.4, 122.3, 128.3, 133.2, 133.8, 144.5, 156.7, 165.4. Anal. Calcd for $C_{12}H_8N_6O$: C, 57.14; H, 3.20; N, 33.32. Found: C, 57.22; H, 3.29; N, 33.25.

*4.2.11. (Z)-2-(1-Methyl-5-nitro-2-oxoindolin-3-ylidene)-2-(1H-tetrazole-5-yl) acetonitrile (**8e**).* Brown powder (0.24 g, yield 79%). Mp 228–230 °C. IR (KBr) (ν_{max}/cm^{-1}): 3153, 2218, 1701, 1581, 1498. MS, *m*/*z*: 297 (M^+). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.36 (br s, NH, overlap with solvent), 3.26 (3H, s, CH_3), 7.13 (2H, d, $^3J_{HH}$=8.6Hz, H–Ar), 8.07 (1H, d, $^3J_{HH}$=8.6 Hz, H–Ar), 8.56 (1H, s, H–Ar). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C (ppm) 26.5, 114.7, 124.1, 125.5, 132.4, 134.5, 135.2, 136.2, 137.8, 138.5, 150.8, 169.7. Anal. Calcd for $C_{12}H_7N_7O_3$: C, 48.49; H, 2.37; N, 32.99. Found: C, 48.42; H, 2.33; N, 32.90.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.12.044.

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