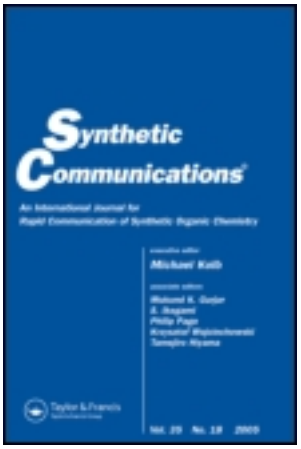

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THREE-COMPONENT REACTION TO FORM 1,4-DIHYDROPYRANO[2,3-*c*]PYRAZOL-5-YL CYANIDES

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The three-component reactions of 3-alkyl-1-phenyl-2-pyrazolin-5-ones, aryl aldehydes, and malononitrile in the presence of base catalysts such as sodium acetate, triethylamine, and magnesium oxide (MgO) are investigated. Magnesium oxide (MgO) effectively catalyzes these reactions to form 1,4-dihydropyrano[2,3-c]pyrazol-5-yl cyanide derivatives. The salient features of this method include high conversions, short reaction times, cleaner reaction profiles, and the use of inexpensive and readily available catalyst.

Keywords: 1,4-Dihydro-pyrano[2,3-*c*]pyrazol-5-yl cyanides; magnesium oxide (MgO); malononitrile; three-component reactions

INTRODUCTION

N-Phenyl-3-substituted 5-pyrazolone derivatives are organic compounds that have been known since 1883; they are very useful as intermediates for pharmaceuticals and are used as anti-inflammatory agents and allergy inhibitors.[1] Also, these 5-pyrazolone derivatives were investigated as thermal stabilizers for rigid polyvinyl chloride (PVC).[2,3] Therefore, great efforts have been directed toward the synthetic manipulation of pyrazolone derivatives to find more useful compounds.[4] In the heterocyclic area, pyrazolones fused to heterocyclic systems such as pyran rings constitute a very important class of compounds. These compounds have been widely used as medicinal intermediates because of their useful biological and pharmacological properties, such as antibacterial, anticoagulant, anticancer, spasmolytic, hypnotic, diuretic, and insecticide.[5–7] Usually 1,4-dihydropyrano[2,3-*c*]pyrazol-5-yl cyanide derivatives have been synthesized in organic solvents and in the presence of an organic base such as pyridine.[8–10] Recently, some new methods have been applied to facilitate these reactions.[11,12] However, some of these methods are limited because of slow reaction rate, poor yields, side products, tedious workup, and the use of toxic solvents or expensive catalysts. In the course of our investigations to develop new synthetic methods in the presence of environmentally friendly base catalysts such as sodium acetate or magnesium oxide (MgO) to reduce the amount of toxic waste and byproducts arising from chemical processes, we have performed

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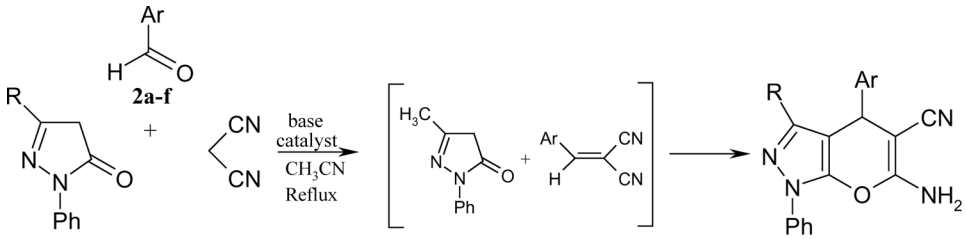


1a-c **3** **4a-i**

a: R= CH_3
b: R= n-propyl
c: R= *iso*-propyl

Scheme 1. Three-component reactions of 3-alkyl-1-phenyl-2-pyrazolin-5-ones, aromatic aldehydes, and malononitrile in the presence of base catalysts.

a one-pot, three-component, highly efficient method for synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazol-5-yl cyanide derivatives catalyzed by magnesium oxide (MgO) as heterogeneous base catalyst in acetonitrile. This strategy includes simple catalyst preparation, mild reaction temperature, easy recovery, and reusability of the catalyst with consistent activity and short reaction times.

RESULTS AND DISCUSSION

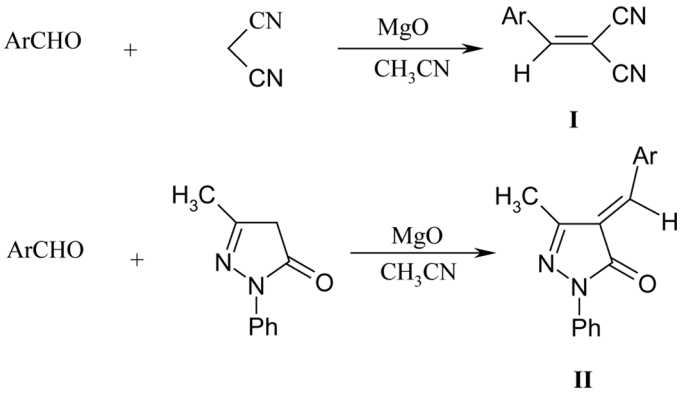
Continuing our ongoing studies on the synthesis of heterocyclic compounds[13–15] in an attempt to obtain the new 1,4-dihydropyrano[2,3-*c*]pyrazol-5-yl cyanide derivatives **4** using multicomponent reactions (MCRs), compounds **4a–i** were prepared from the three-component reaction of 3-alkyl-1-phenyl-2-pyrazolin-5-ones **1a–c** aromatic aldehydes **2** and malononitrile **3** in the presence of base catalysts (Scheme 1).

Table 1. Synthesis of **4a–i** in the presence of base catalysts

			Sodium acetate $EtOH/H_2O$		Et_3N acetonitrile		CM[a]/HSA[b] (MgO)		
Compound	Ar	R	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (min)	Yield (%)	Mp [ref.] (°C)
4a	C_6H_5	CH_3	3	81	8	83	180/22	83/95	170–171[8]
4b	CH_3	4-MeC_6H_4	3	80	7.5	85	180/35	85/93	176–178[8]
4c	4-$MeOC_6H_4$	CH_3	3.5	77	7	75	180/25	75/90	171–172[8]
4d	4-ClC_6H_4	CH_3	2	85	6	87	120/12	87/96	174–175[11]
4e	2,4-ClC_6H_3	CH_3	1.5	85	8.5	88	90/15	88/92	184–186[11]
4f	4-BrC_6H_4	CH_3	4	76	7	76	210/40	76/88	184–185[12]
4g	4-ClC_6H_4	Propyl	2	87	7	88	120/22	88/92	181–182
4h	4-ClC_6H_4	*Iso*-propyl	2	89	6	87	120/20	87/93	172–173
4i	2,4-ClC_6H_3	*Iso*-propyl	1.5	90	8	85	90/18	85/95	188–189

[a]Commercial MgO.
[b]High-surface-area MgO.

Table 2. Knoevenagel condensation of aldehydes with malononitrile or 3-methyl-1-phenyl-5-pyrazolone in CH_3CN in the presence MgO

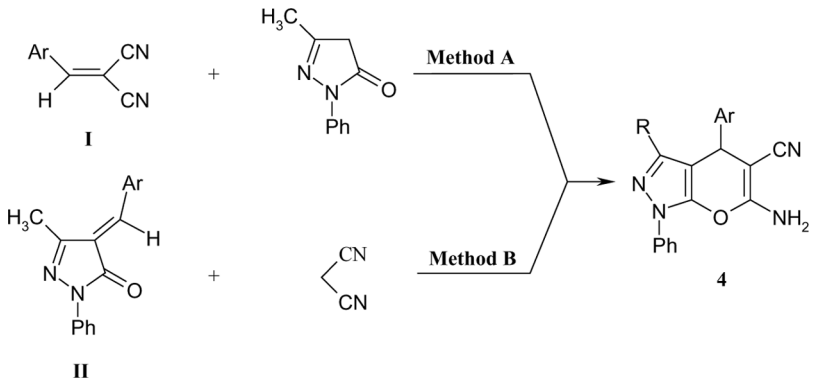


Compound	Ar	Time	Yield (%)	Mp [ref.] (°C)
Ia	C_6H_5	5 min	91	82–83[19]
IIa	C_6H_5	3 h	95	110–111[18]
Ib	4-ClC_6H_4	2 min	93	156–158[19,20]
IIb	4-ClC_6H_4	2 h	96	107–108[18]
Ic	4-$MeOC_6H_4$	7 min	87	113–115[19,20]
IIc	4-$MeOC_6H_4$	3 h	90	124–125[18]

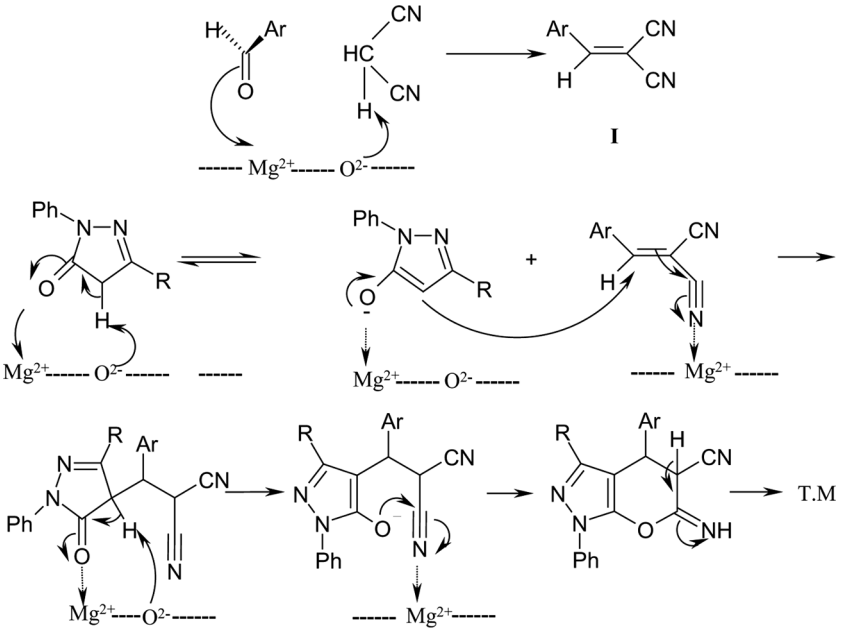
As shown in Table 1, yield of the reaction is markedly affected by the catalyst and solvent, and optimum results were obtained when reactions were treated in acetonitrile and in the presence of high-surface-area MgO. These reactions occur fast, within a few minutes (18–40 min), and give excellent yields (88–95%) of products **4a**–**i** with high purity. The same reactions have been reported for synthesis of compounds **4a**–**f** using *p*-dodecylbenzenesulfonic acid (DBSA) or sulfamic acid as a catalyst in longer reaction times (approximately 3 h) and lower yields.[11,12] Because the three-component reaction of malononitrile, aromatic aldehydes, and pyrazoles involve both Knoevenagel condensation and Michael addition, we studied separately Knoevenagel condensations of malononitrile as active methylene compounds with aromatic aldehydes **2a**–**c**. The Knoevenagel condensations of malononitrile with aldehydes have been extensively studied, and the rate of these reactions are fast, whereas the condensation of 3-methyl-1-phenyl-5-pyrazolone **1a** with aromatic aldehydes has been reported in poor yields and long reaction times in the presence of catalysts such as ethylenediammonium diacetate (EDDA) or ionic liquids [Bmim]BF_4 and [Bmim]PF_6.[16–18] In this research, to compare the rate of the reaction of these two Knoevenagel condensations, magnesium oxide (MgO) was used as a catalyst, and the results of these reactions are presented in Table 2.

We also studied separately the Michael addition of arylidenemalononitriles **I** with pyrazolone **1a** and 5-methyl-2-phenyl-4-arylmethylidene-2,4-dihydro-3*H*-pyrazol-3-ones **II** with malononitrile, which afforded the same product of 1,4-dihydropyrano[2,3-*c*]pyrazol-5-yl cyanide derivatives in the presence MgO. As shown in Table 3, the rates of these reactions are fast.

Table 3. Michael additions of 3-methyl-1-phenyl-5-pyrazolone with compounds **I** and compounds **II** with malononitrile were catalyzed by MgO in CH_3CN



Compound	Ar	METHOD	Time (min)	Yield (%)
4a	C_6H_5	A	20	95
4a	C_6H_5	B	12	96
4c	4-$MeOC_6H_4$	A	25	90
4c	4-$MeOC_6H_4$	B	15	92
4d	4-ClC_6H_4	A	12	96
4d	4-ClC_6H_4	B	5	96



Scheme 2. Mechanism for the formation of compounds **4**.

As expected, on the basis of the results shown in Tables **2** and **3**, first the arylidenemalononitriles **I** containing an electron-poor C=C double bond are produced by rapid Knoevenagel condensation of malononitrile with the aromatic aldehydes [the formation of the compounds **I** was monitored by thin-layer chromatography, TLC (*n*-hexane/diethyl ether as eluent)]. The second step is followed by Michael addition, cycloaddition, and isomerization to afford the 1,4-dihydropyrano[2,3-*c*]-pyrazol-5-yl cyanide derivatives **4** (Scheme 2).

Compounds **4a**–**f** are known in the literature.[8–12] The infrared (IR) spectra and melting points of all known compounds were consistent with those reported in the literature. Structures **4g**–**i** were established on the basis of IR measurements, which showed the presence of CN at 2235–2238 cm^{-1} and two sharp bands at 3500–3450 and 3390–3380 cm^{-1} due to asymmetric and symmetric vibrations of the NH_2 group. The ^1H and ^{13}C NMR and mass spectra were also in accordance with the proposed structures.

In conclusion, we have developed a simple and efficient method for the synthesis of pyrazoles having a pyran nucleus in the presence of MgO, a highly effective heterogeneous base catalyst. Advantages of the strategy include simple catalyst preparation, mild reaction temperature, easy recovery, and reusability of the catalyst with consistent activity and short reaction times.

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting-point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 Fourier transform (FT)–IR spectrometer. The proton and carbon NMR spectra were recorded with a Bruker DRX-500 Avance spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Preparation of High-Surface-Area MgO

The catalyst used in this study was obtained by dehydrated $Mg(OH)_2$ at 450°C for 2 h. A calcination temperature of 400–500°C gave maximum conversion. When the catalyst was calcined above 500°C, the activity of MgO decreased and continued to decrease as the calcination temperature increased. The maximum surface area was obtained after calcining the calcining the samples at 400–500°C.[21]

6-Amino-4-aryl-3-alkyl-1-phenyl-1,4-dihydropy-rano[2,3-*c*]pyrazol-5-yl cyanide Derivatives (**4a**–**i**)

A mixture of the aldehyde (2 mmol), 3-alkyl-1-phenyl-2-pyrazolin-5-ones (2 mmol), malononitrile (2 mmol), and sodium acetate (2 mmol) in H2O (10 mL) and ethanol (20 mL) or triethylamine (four or five drops) in acetonitrile (30) or MgO (0.05 g) in acetonitrile (30 mL) was refluxed with stirring for the time reported in Table 1. (The progress of the reaction was monitored by TLC, and hexane/ethyl acetate was used as an eluent.) After completion of the reaction, the catalyst was separated from the reaction mixture by centrifugation. The excess acetonitrile

was removed by evaporation and poured into ice-cold water; the crude product was filtered, dried, and recrystallized from 96% ethanol.

6-Amino-4-(4-chlorophenyl)-1-phenyl-3-propyl-1,4-dihydropyrano[2,3-*c*]-pyrazol-5-yl cyanide (4g). Pale yellow crystals (0.71 g), yield 0.92%; mp 181–182°C; ν_{max} (KBr): 3456, 3312 (NH_2), 2210 (CN), 1656 (C=N), 1586 (Ar) cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.83–7.30 (9H, m, arom), 7.24 (2H, s, NH_2), 4.73 (1H, s, CH), 2.14 (1H, m, H_a on C_1 of propyl), 2.05(1H, m, H_b on C_1 of propyl), 3.5 (1H, m, H_a on C_2 of propyl), 1.22 (1H, m, H_b on C_2 of propyl), 1.83 (3H, t, CH_3); δ_C (125 MHz, DMSO-d6) 160.20 (C6), 146.82, 144.74, 143.87, 183.40, 132.45, 130.60, 130.19, 129.36, 127.10, 120.97, 120.73, 98.64 (CN), 58.82 (C5), 39.90 (C4), 9.73, 21.56, 14.51. MS, m/z (%): 390 (M^+, 15), 324 (10), 280 (23), 279 (100), 127 (10), 77 (65). Anal. calcd. for $C_{22}H_{19}ClN_4O$: C, 67.60; H, 4.90; N, 14.33%. Found: C, 67.39; H, 4.78; N, 14.03.

6-Amino-4-(4-chlorophenyl)-3-isopropyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-5-yl cyanide (4h). Pale yellow crystals (0.72 g), yield 0.93%, mp 172–173°C, ν_{max} (KBr): 3456, 3312 (NH_2), 2210 (CN), 1656 (C=N), 1586 (Ar) cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.80 (2H, d, $^3J_{HH} = 8.05$ Hz, CH), 7.50 (2H, t, $^3J_{HH} = 7.7$ Hz, CH, arom), 7.41 (2H, d, $^3J_{HH} = 8.39$ Hz, CH, arom), 7.33 (2H, t, $^3J_{HH} = 7.44$ Hz, CH, arom), 7.31 (2H, d, $^3J_{HH} = 8.05$ Hz, CH, arom), 7.22 (2H, s, NH_2), 4.77 (1H, s, CH), 2.44 (1H, m, CH),1.02 (3H, d, $^3J_{HH} = 6.95$, CH_3), 0.85 (3H,d,$^3J_{HH} = 6.88$, CH_3), (125 MHz, DMSO-d6) 160.00 (C6), 154.60, 144.86, 144.17, 138.44, 132.45, 130.61, 130.18, 129.39, 127.11, 121.07, 120.72, 97.77 (CN), 59.10 (C5), 39.90 (C4), 37.22, 27.72, 22.34, 21.31. MS, m/z (%): 390 (M^+, 17), 324 (17), 280 (30), 279 (100), 127 (25), 77 (70). Anal. calcd. for $C_{22}H_{19}ClN_4O$: C, 67.60; H, 4.90; N, 14.33%. Found: C, 67.31; H, 4.74; N, 14.06.

6-Amino-4-(2,4-dichlorophenyl)-3-isopropyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-5-yl cyanide (4i). White crystals (0.8 g), yield 0.95%, mp 188–189°C, ν_{max} (KBr): 3438, 3321, 3204 (NH_2), 2197 (CN), 1659 (C=N), 1589 (Ar) cm^{-1}; δ_H (500 MHz, DMSO-d_6): 7.81–7.32 (8H, m, arom), 7.31 (2H, s, NH_2), 5.21 (1H, s, CH), 2.43 (1H, m,CH), 1.03 (3H, d, $^3J_{HH} = 6.95$, CH_3), 0.86 (3H, d, $^3J_{HH} = 6.88$, CH_3), δ_C (125 MHz, DMSO-d6) 160.12 (C6), 154.02, 144.40, 143.56, 143.02, 138.38, 132.55, 130.40, 130.28, 130.02, 129.30, 127.19, 121.12, 104.50 (CN), 58.34 (C5), 38.01 (C4), 27.91, 22.26, 21.31. MS, m/z (%): 425 (M^+, 12), 361 (22), 335 (27), 314(100), 77 (76). Anal. calcd. for $C_{22}H_{18}Cl_2N_4O$: C, 62.13; H, 4.27; N, 13.17%. Found: C, 61.81; H, 4.16; N, 12.88.

Knoevenagel Condensation

General procedure for the preparation of arylidenemalononitriles Ia–c. The reactions were carried out in a standard round-bottom glass flask equipped with a vertical condenser under thermal conditions. Reactions were performed with arylaldehydes **1** (2 mmol), malononitrile **2** (2 mmol), and MgO (0.05 g) in acetonitrile (40 mL) as solvent, refluxed with stirring for the specified time (Table 1).

General procedure for the preparation of 5-alkyl-2-phenyl-4-arylmethylidene-2,4-dihydro-3*H*-pyrazol-3-ones IIa–c. The reactions were carried out in a standard round-bottom glass flask equipped with a vertical condenser under thermal conditions. Reactions were performed with arylaldehydes **1** (2 mmol), 3-methyl-1-phenyl-2-pyrazolin-5-one (2 mmol), and MgO (0.05 g) in acetonitrile (40 mL) as solvent, refluxed with stirring for the specified time (Table 1).

Michael addition. Reactions were performed with benzylidenemalononitrile **1** (2 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (2 mmol) [method A] or 1-phenyl-3-methyl-4-arylmethylene-5-pyrazolones and malononitrile (2 mmol) [method B] using MgO (0.05 g) as a base catalyst in acetonitrile (40 mL), refluxed with stirring for the appropriate time (Table 2). The product **4** was precipitated from the reaction mixture by cooling, and the solid was filtered and recrystallized from ethanol.

3-Methyl-1-phenyl-4-(1-phenylmethylidene)-1*H*-pyrazol-5-one (IIa). Red crystals (0.49 g), yield 92%; mp 108–110°C; ($_{max}$ (KBr):1682 (C=O), 1618 (C=N); δ_H (500 MHz, DMSO-d_6): 8.55 (2H, d, $^3J_{HH} = 7.37$ Hz, arom); 7.86 (2H, d, $^3J_{HH} =$ 7.69 Hz, arom); 7.79 (1H, s, =CH), 7.54–7.15 (6H,m, arom), 2.31 (3H, s, CH_3); δ_C (125 MHz, DMSO-d_6): 162.31 (C=O), 152.68 (C=N), 149.16,139.01, 134.52, 134.06, 133.78, 129.71, 129.51, 127.58, 125.49, 119.24, 13,98; MS, *m/z* (%): 262 (M+, 30), 182 (38), 128 (22), 101 (8), 91 (10), 77 (40), 59 (25), 51 (20), 43 (100). Anal. calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68%. Found: C, 77.61; H, 5.22; N, 10.41.

4-(1-(4-Methyoxyphenyl)methylidene)-3-methyl-1-phenyl-1*H*-pyrazole-5-one (IIb). Orange crystals (0.52 g), yield 90%; mp 125–127°C; ($_{max}$ (KBr): 1682 (C=O), 1589 (C=N); δ_H (500 MHz, DMSO-d_6): 8.66 (2H, d,$^3J_{HH} = 7.37$ Hz, arom), 7.89 (2H,d, $^3J_{HH} = 7.69$ Hz, arom), 7.71 (1H, s, =CH), 7.39 (2H, t, $^3J_{HH} = 7.4$ Hz, arom), 7.14 (2H, t,$^3J_{HH} = 7.24$ Hz, arom), 7.09 (2H, d, $^3J_{HH} = 8.93$ Hz, arom), 3.85 (3H, s, –OCH3), 2.28 (s, 3H, $-CH_3$); δ_C (125 MHz, DMSO-d_6): 164.50 (C=O), 162.72 (C=N), 152.66, 148.95, 139.24, 137.7, 129.66, 127.04, 125.29, 124.63, 119.18, 115.22, 56.59, 13.99; MS, *m/z* (%): 292 (M+, 100), 185 (52), 159 (48), 146 (14), 128 (19), 115 (45), 91 (32), 77 (72), 63 (20), 51 (35), 57 (35), 44 (53), 41 (34). Anal. calcd. for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58%. Found: C, 73.74; H, 5.46; N, 9.32.

4-(1-(4-Chlorophenyl)methylidene)-3-methyl-1-phenyl-1*H*-pyrazole-5-one (IIc). Red crystals (0.55 g), yield 93%; mp 109–110°C; ($_{max}$ (KBr):1653 (C=O), 1589 (C=N); δ_H (500 MHz, DMSO-d_6): 8.55 (2H, d,$^3J_{HH} = 8.61$ Hz, arom), 7.84 (2H, d, $^3J_{HH} = 8.15$ Hz, arom), 7.74 (1H, s, =CH), 7.57 (2H, d, $^3J_{HH} = 8.16$ Hz, arom) 7.38 (2H, t,$^3J_{HH} = 7.56$ Hz, arom), 7.16 (2H, t, $^3J_{HH} = 7.33$ Hz, arom), δ_C (125 MHz, DMSO-d_6): 162.22. (C=O), 153.56 (C=N), 147.42, 138.91, 138.73, 136.16, 132.60, 129.68, 129.61, 127.97, 125.52, 119.21, 13.92; MS, *m/z* (%): 296 (M+, 100), 185 (100), 128 (25), 77 (48). Anal. calcd. for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44%. Found: C, 98.45; H, 4.20; N, 9.12.

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