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Synthesis and antimicrobial activity of pyrazole derivatives *via* 1,3-dipolar cycloaddition of nitrile imines with ethyl acetoacetate

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The ethyl acetoacetate reacts with the nitrile imines generated *in situ* by the catalytic dehydrogenation of diphenyl hydrazones using chloramine-T (CAT) to afford regioselective cycloadducts in 80% yields respectively. The structures of these compounds have been characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques and elemental analysis. All the pyrazole derivatives have been tested for their antibacterial and antifungal activities.

Key words: 1,3-dipolar cycloaddition, nitrile imines, pyrazoles.

INTRODUCTION

Heterocyclic compounds are considered as the most promising molecules for the design of new drugs. 1,3-Dipolar cycloaddition reactions are an efficient synthetic tool for constructing biologically potent five membered heterocyclic compounds [1, 2]. Pyrazoles, pyrazolines, pyrazolidines and pyrazolones are gaining importances as biologically active compounds possessing such as analgesic, antipyretic, antiinflammatory, germicidal and antifungal activities [3, 4], antiprotozoal [5], fungicidal [6], bactericidal [6], herbicidal and plant growth regulating properties.

Apart from the various dipolar reagent nitrile imines are used in numerous 1,3-dipolar cycloaddition reaction leading to pyrazoles, pyrazolines, pyrazolidines and other heterocyclic compounds [7]. Huisgen and co-workers first reported [8] the authentic in situ generation of nitrile imines by the thermolysis of 2,5-diphenyl tetrazole in the presence of ethyl phenyl propiolate and obtained 2,3,5-triphenyl carbethoxypyrazole. The usual synthesis of nitrile imines involves the thermolysis or photolysis of tetrazole [8], oxidation of aldehyde hydrazones with lead tetra acetate [9], CAT [10] and mercuric acetate [11].

In addition to this, nitrile imines are known to react with heterocyclic compounds to yield a variety of polyheterocycles [12]. Shawali and co-workers [13] prepared a numerous pyrazole derivatives by the reaction of *in situ* generated nitrile imines obtained from hydrazidoyl halides with sodium salt of active methylene compounds, such as *β*-ketosulphones, *β*-ketoanilides and *β*-cyanoketones. Baruah *et al.* [14] generated the *C*-acetyl and *C*-ethoxycarbonyl nitrile imines *in situ* from the corresponding hydrazonoyl halides in the presence of dry triethylamine in anhydrous chloroform, and have used these nitrile imines for the preparation of pyrazoles derivatives. The intramolecular cycloaddition of *in situ* generated nitrile imine with aldonitrones afforded triazoles [15]. Mogilaiah *et al.* [16] developed a solvent free method for the facile synthesis of 1,8-naphthyridinyl-pyrazoles using $POCl_3$-DMF (Vilsmeier-Haack reagent) over silica gel under microwave irradiation. Aly *et al.* [17] showed a new synthetic route for the synthesis of some pyrazole derivatives from 3-aryl-1-phenyl-*1H*-pyrazole-4-carbaldehydes.

Padmavathi and co-workers [18] prepared activated *bis* pyrazolines and *bis* isoxazolines by 1,3-dipolar cycloaddition of nitrile imines and nitrile oxides to activated *bis* olefinic systems in the presence of Chloramine-T. Bacchetti [19] prepared 1,4-dicarboethoxy pyrazoles by intermolecular cycloaddition of nitrile imines with ethyl acetoacetate. Though there are more references available in the literature on cycloaddition of nitrile imines with alkenes and alkyne, there is a less information about the use of keto-enol tautomers as dienophile for the cycloaddition. We have synthesized [20] the 1-(5-methyl-1,3-diphenyl-1*H*-pyrazol-4-yl)-ethanone in quantitative yield *via* 1,3-dipolar cycloaddition of enol form of acetyl acetone with the nitrile imines generated *in situ* by the catalytic dehydrogenation of diphenyl hydrazones using CAT. This prompted us to work in this area in detail to make it as a general method for the synthesis of pyrazoles derivatives.

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RESULTS AND DISCUSSION

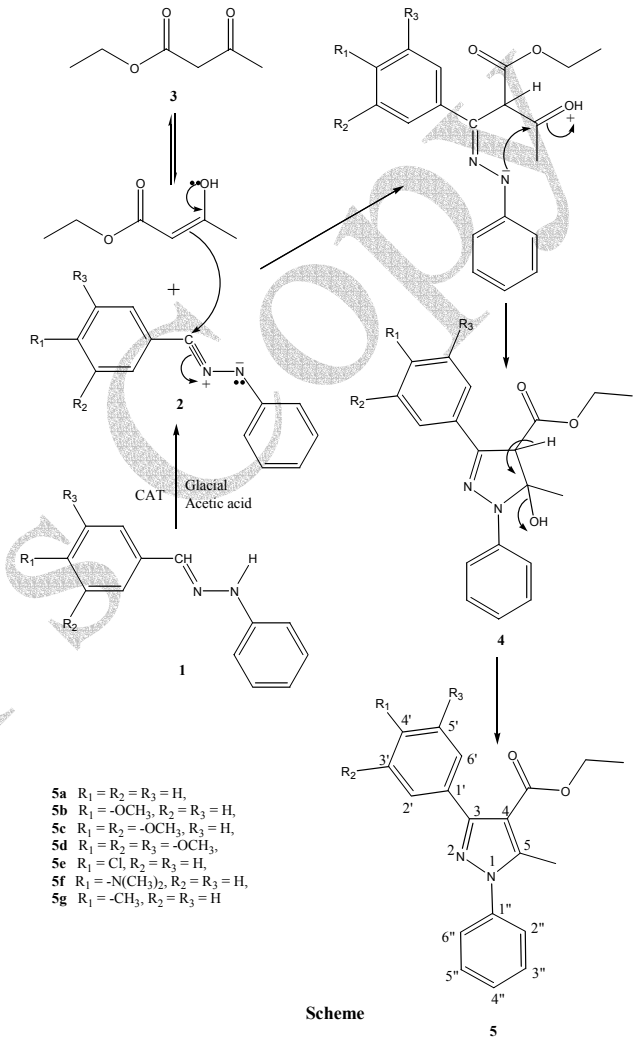
It is well known that acetyl acetone and ethyl acetoacetate exist in two dynamic equilibrium states *via*, keto and enol forms. It is also known that typical cycloaddition of nitrile imines with alkenes and alkynes afford pyrazolines and pyrazoles respectively. It is interesting to note that, though the expected products are pyrazolines as similar to that of addition of nitrile imines to alkenes, the reaction afforded pyrazoles with loss of water molecule (Scheme).

In typical reaction, a mixture of aldehyde hydrazone **1a** with excess of ethyl acetoacetate **3** and CAT in glacial acetic acid was stirred at room temperature for about 2–3 hours. After the usual work up, **5a** was isolated as light yellow oil in 80% yield. In similar manner, **1b–g** were converted into the corresponding pyrazole derivatives **5b–g** in good yields. IR, ^{1}H NMR, ^{13}C NMR, MS studies and elemental analysis provide the structural proof for the products. In ^{1}H NMR spectra, the signals for the ethoxy protons appears as a quartet in the region δ 4.12–4.31 ppm, (2H, J = 7.2 Hz, –O<u>C</u>H$_2$–CH$_3$), while the protons for the methyl group at C-5 appear as a singlet in the region δ 2.68–2.75 ppm. The downward shift of the methyl group at the C-5 is probably due to deshielding by the –CO–OC$_2$H$_5$ group. These observations clearly indicate that the formation of the cycloadduct **5a** is obtained *via* pyrazolines **4** with the loss of water molecule. In ^{13}C NMR spectra, the –C-3 and C-4 appear as singlet (decoupled) in the region δ 160.82–161.14 and δ 108.32–118.86 ppm respectively, C-5 appear as singlet in the region δ 176.14–176.26 ppm. All cycloadducts showed M+1 as a base peak in the mass spectra. Further, the elemental analysis supported the formation of the products.

ANTIMICROBIAL SCREENING

Synthesized pyrazoles (**5a–g**) were screened (dose of 100 μg) for their antibacterial activity against Gram-negative bacteria *Escherichia coli (E. coli)* and Gram-positive bacteria *Staphylococcus aureus* (*S. aureus*) using filter paper disc method [21]. Plates inoculated with *E. coli* were incubated for 48 h and plates inoculated with *S. aureus* for 24 h respectively at room temperature. *Streptomycin sulphate* was used as a standard. After the period of incubation the inhibition zones were measured in mm and results obtained are shown in Table 1. All the compounds were also screened (dose of 100 μg) for their antifungal activity against *Candida albicans* (*C. albicans*) and *Aspergillus niger* (*A. niger*) using *Griseofulvin* as a standard. The results are shown in Table 1.

Compared with *Streptomycin sulphate* the compounds **5b** and **5e–g** showed moderate antibacterial activity against *E. coli* and **5b** and **5f** against *S. aureus*. Compared with the standard *Griseofulvin* the compounds **5b–c, 5e** and **5f** showed promising antifungal activity against *C. albicans* and **5f** against *A. niger*.



Scheme

Table 1. Antibacterial and antifungal activity of synthesized pyrazole derivatives (**5a–g**). (Zone of inhibition in mm).

Compounds	Antibacterial activity		Antifungal activity	
	E. coli	*S. aureus*	*C. albicans*	*A. niger*
5a	08	10	06	06
5b	12	12	08	06
5c	10	08	08	04
5d	10	08	06	04
5e	12	10	08	06
5f	14	12	10	08
5g	12	10	06	04
Streptomycin sulpate	18	20	Not tested	Not tested
Griseofulvin	Not tested	Not tested	14	12

EXPERIMENTAL SECTION

The purity of all synthesized compounds was checked by thin layer chromatography using silica gel G. The final compounds were purified by column chromatography on silica gel (70–230 mesh, Merck) using mixture of chloroform:acetone (7:1) as eluent. ^{1}H NMR spectra were registered either on a Bruker 300 MHz or Jeol 60 MHz Hitachi Perkin Elmer spectrometer, and ^{13}C NMR spectra on a Jeol GSX 400 (75 MHz) instrument using 1% tetramethylsilane in $CDCl_3$ as an internal standard (chemical shifts are expressed in δ, ppm downfield from the tetramethylsilane). Mass spectra were obtained on an electron impact Maspec MSW 9629 spectrometer and important fragments are given with the relative intensities in brackets.

Typical procedure for the preparation of ethyl 5-methyl-1,3-diphenyl-1H-pyrazole-4-carboxylate (**5a**): A mixture of benzaldehyde hydrazone (**1a**, 2.35 g, 12.0 mmol), excess of freshly distilled ethyl acetoacetate **3** (2.6 g, 20.0 mmol) and CAT (3.94 g, 14.0 mmol) in glacial acetic acid (25 ml) were stirred at room temperature for 2–3 h. The progress of the reaction was monitored by TLC. After the completion of the reaction the residue was dissolved in ether (25 ml), washed successively with water (2 × 20 ml), 1 N NaOH (1 × 10 ml), brine solution (2 × 15 ml) and dried over Na_2SO_4. Evaporation of the solvent afforded crude oily substance. Purification was done by column chromatography using a mixture of dichloromethane:ethyl acetate (8:1) as eluent, which afforded **5a** as light yellow oil in 80% yield (2.93 g). The pyrazole **5a** showed IR bands (Nujol) ν: 1722 cm^{-1} (C=O), 1620 cm^{-1} (C=N), 1602 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, 3H, J = 7.2 Hz, –OCH_2–$\underline{C}H_3$), 2.72 (s, 3H, H_3C–C(5)), 4.18 (q, 2H, J = 7.2 Hz, –O$\underline{C}H_2$–CH_3), 7.05–7.26 (s, 5H, Ar'–H), 7.65–7.78 (m, 5H, Ar"–H); ^{13}C NMR ($CDCl_3$) δ: 0.92 (q, 1C, H_3C–C(5)), 13.56 (q, 1C, –CH_2–$\underline{C}H_3$), 58.62 (t, 1C, –$\underline{C}H_2$–), 108.32 (s, 1C), 118.08 (d, 2C), 124.42 (d, 1C), 124.56 (d, 2C), 126.22 (d, 2C), 128.74 (d, 2C), 130.28 (s, 1C), 131.08 (d, 1C), 132.42 (s, 1C), 161.12 (s, 1C), 176.22* (s, 1C, 5-C), 174.88* (s, 1C, CO). MS (relative intensity) m/e for $C_{19}H_{18}N_2O_2$: 307 (M+1, 100), 277(31), 233 (38), 218 (21), 194 (25), 112 (18), 103 (75), 91 (44), 88 (10), 29(22). Anal. Calcd: C, 74.49; H, 5.92; N, 9.14%. Found: C, 74.36; H, 5.72; N, 9.08%.

Ethyl 3-(4-methoxyphenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**5b**): Obtained from 4-methoxybenzaldehyde hydrazone **1b** (2.71 g, 12 mmol), ethyl acetoacetate (2.6 g, 20.0 mmol) as an oily substance in 78% yield (3.14 g). IR bands (Nujol) ν: 1716 cm^{-1} (C=O), 1618 cm^{-1} (C=N), 1596 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H, J = 6.9 Hz, –OCH_2–$\underline{C}H_3$), 2.75 (s, 3H, H_3C–C(5)), 3.78 (s, 3H, –OCH_3), 4.12 (q, 2H, J = 7.0 Hz, –O$\underline{C}H_2$–CH_3), 6.92 (d, 2H, Ar'–H), 7.22 (d, 2H, Ar'–H), 7.36–7.48 (m, 5H, Ar"–H); ^{13}C NMR ($CDCl_3$) δ: 0.86 (q, 1C, H_3C–C(5)), 13.54 (q, 1C, –CH_2–$\underline{C}H_3$), 55.80 (q, 1C, 4'–OCH_3), 58.62 (t, 1C, –$\underline{C}H_2$–), 108.52 (s, 1C), 118.18 (d, 2C), 122.56 (d, 2C), 124.88 (d, 1C), 126.22 (d, 2C), 128.74 (d, 2C), 136.28 (s, 1C), 131.08 (d, 1C), 132.42 (s, 1C), 160.82 (s, 1C), 176.20* (s, 1C, 5-C), 171.68* (s, 1C, CO). MS (relative intensity) m/e for $C_{20}H_{20}N_2O_3$: 337 (M+1, 100), 307(32), 263 (40), 248 (20), 224 (24), 112 (16), 133 (78), 91 (46), 88 (10), 29(24). Anal. Calcd: C, 71.41; H, 5.99; N, 8.33%. Found: C, 71.38; H, 5.87, N; 8.25%.

Ethyl 3-(3,4-dimethoxyphenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**5c**). Obtained from 3,4-dimethoxybenzaldehyde hydrazone **1c** (2.56 g, 10 mmol), ethyl acetoacetate (2.34 g, 18.0 mmol) as an oily substance in 82% yield (2.74 g). IR bands (Nujol) ν: 1720 cm^{-1} (C=O), 1622 cm^{-1} (C=N), 1596 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H, J = 7.0 Hz, –OCH_2–$\underline{C}H_3$), 2.68 (s, 3H, H_3C–C(5)), 3.75 (s, 6H, –OCH_3), 4.16 (q, 2H, J = 7.1 Hz, –O$\underline{C}H_2$–CH_3), 6.98–7.12 (m, 3H, Ar'–H), 7.48–7.66 (m, 5H, Ar"–H); ^{13}C NMR ($CDCl_3$) δ: 1.02 (q, 1C, H_3C–C(5)), 13.66 (q, 1C, –CH_2–$\underline{C}H_3$), 55.76* (q, 1C, 4'–OCH_3), 55.84* (q, 1C, 3'–OCH_3), 59.02 (t, 1C, –$\underline{C}H_2$–), 108.86 (s, 1C), 118.28 (d, 2C), 122.52 (d, 2C), 124.86 (d, 1C), 126.34 (d, 2C), 128.78 (d, 2C), 136.36 (s, 1C), 131.12 (d, 1C), 132.44 (s, 1C), 161.14 (s, 1C), 176.24* (s, 1C, 5-C), 171.72* (s, 1C, CO). MS (relative intensity) m/e for $C_{21}H_{22}N_2O_4$: 367 (M+1, 100), 337(30), 293 (39), 278 (23), 254 (28), 163 (76), 112 (14), 91 (46), 88 (12), 29(26). Anal. Calcd: C, 68.84; H, 6.05; N, 7.65%. Found: C, 68.77; H, 5.96; N, 7.54%.

Ethyl 5-methyl-1-phenyl-3-(3,4,5-trimethoxyphenyl)-1H-pyrazole-4-carboxylate (**5d**). Obtained from 3,4,5-trimethoxybenzaldehyde hydrazone **1d** (2.86 g, 10 mmol), ethyl acetoacetate (2.34 g, 18.0 mmol) as an oily substance in 81% yield (3.20 g). IR bands (Nujol) ν: 1718 cm^{-1} (C=O), 1620 cm^{-1} (C=N), 1600 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, 3H, J = 7.1 Hz, –OCH_2–$\underline{C}H_3$), 2.70 (s, 3H, H_3C–C(5)), 3.71 (s, 9H, –OCH_3), 4.22 (q, 2H, J = 7.2 Hz, –O$\underline{C}H_2$–CH_3), 6.96 (m, 2H, Ar'–H), 7.52–7.68 (m, 5H, Ar"–H); ^{13}C NMR ($CDCl_3$) δ: 1.04 (q, 1C, H_3C–C(5)), 13.62 (q, 1C, –CH_2–$\underline{C}H_3$), 56.6 (q, 2C, 3',5'–OCH_3), 58.4 (q, 1C, 4'–OCH_3), 59.22 (t, 1C, –$\underline{C}H_2$–), 108.66 (s, 1C), 122.28 (d, 2C), 124.66 (d, 1C), 126.48 (d, 2C), 128.56 (d, 2C), 136.54 (s, 1C), 131.24 (d, 1C), 132.46 (s, 1C), 136.12 (d, 2C), 161.04 (s, 1C), 176.22* (s, 1C, 5-C), 169.88* (s, 1C, CO). MS

(relative intensity) m/e for $C_{22}H_{24}N_2O_5$: 397 (M+1, 100), 367(29), 323 (42), 308 (24), 284 (22), 193 (76), 112 (21), 91 (46), 88 (14), 29(30). Anal. Calcd: C, 66.65; H, 6.10; N, 7.07%. Found: C, 66.56; H, 5.98; N, 7.04%.

Ethyl 3-(4-chlorophenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**5e**)**.** Obtained from 4-chlorobenzaldehyde hydrazone **1e** (2.76 g, 12 mmol), ethyl acetoacetate (2.6 g, 20.0 mmol) as an oily substance in 79% yield (3.21g). IR bands (Nujol) ν: 1724 cm^{-1} (C=O), 1616 cm^{-1} (C=N), 1598 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 3H, *J* = 7.2 Hz, $–OCH_2–\underline{C}H_3$), 2.74 (s, 3H, $H_3C–C(5)$), 4.22 (q, 2H, *J* = 7.1 Hz, $–O\underline{C}H_2–CH_3$), 6.98 (d, 2H, Ar'–H), 7.18 (d, 2H, Ar'–H), 7.44–7.60 (m, 5H, Ar"–H); ^{13}C NMR ($CDCl_3$) δ: 1.02 (q, 1C, $H_3C–C(5)$), 13.58 (q, 1C, $–CH_2–\underline{C}H_3$), 59.22 (t, 1C, $–\underline{C}H_2–$), 108.48 (s, 1C), 123.36 (d, 2C), 124.36 (d, 1C), 127.22 (d, 2C), 128.62 (d, 2C), 134.62 (d, 1C), 132.46 (s, 1C), 136.12 (d, 2C), 138.14 (s, 1C), 161.84 (s, 1C), 176.14* (s, 1C, 5-C), 169.88* (s, 1C, CO). MS (relative intensity) m/e for $C_{19}H_{17}N_2O_2Cl$: 341 (M+1, 100), 311 (30), 267 (41), 252 (18), 228 (34), 137 (76), 112 (16), 91 (42), 88 (12), 29(26). Anal. Calcd: C, 66.96; H, 5.03; N, 8.22%. Found: C, 66.91; H, 4.90; N, 8.16%.

Ethyl 3-(4-N,N-dimethylaminophenyl)-5-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**5f**). Obtained from 4-*N,N*-dimethylbenzaldehyde hydrazone **1f** (2.86 g, 12 mmol), ethyl acetoacetate (2.6 g, 20.0 mmol) as an oily substance in 78% yield (3.25 g). IR bands (Nujol) ν: 1728 cm^{-1} (C=O), 1624 cm^{-1} (C=N), 1602 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, 3H, *J* = 6.9 Hz, $–OCH_2–\underline{C}H_3$), 2.68 (s, 3H, $H_3C–C(5)$), 2.98 (s, 6H, $–N(CH_3)_2$), 4.31 (q, 2H, *J* = 6.8 Hz, $–O\underline{C}H_2–CH_3$), 7.08 (d, 2H, Ar'–H), 7.24 (d, 2H, Ar'–H), 7.48–7.66 (m, 5H, Ar"–H); ^{13}C NMR ($CDCl_3$) δ: 1.04 (q, 1C, $H_3C–C(5)$), 13.62 (q, 1C, $–CH_2–\underline{C}H_3$), 44.36 (q, 2C, $–N(CH_3)_2$), 59.28 (t, 1C, $–\underline{C}H_2–$), 108.38 (s, 1C), 123.16 (d, 2C), 124.30 (d, 1C), 127.44 (d, 2C), 128.56 (d, 2C), 130.04 (d, 2C), 132.46 (s, 1C), 134.78 (d, 1C), 138.24 (s, 1C), 161.12 (s, 1C), 176.26* (s, 1C, 5-C), 169.36* (s, 1C, CO). MS (relative intensity) m/e for $C_{21}H_{23}N_3O_2$: 350 (M+1, 100), 320 (28), 276 (42), 261 (22), 237 (26), 146 (74), 112 (22), 91 (40), 88 (14), 29(30). Anal. Calcd: C, 72.18; H, 6.63; N, 12.03%. Found: C, 72.12; H, 6.51; N, 11.96%.

Ethyl 5-methyl-1-phenyl-3-p-tolyl-1H-pyrazole-4-carboxylate (**5g**). Obtained from 4-methylbenzaldehyde hydrazone **1g** (2.10 g, 10 mmol), ethyl acetoacetate (2.08 g, 16.0 mmol) as an oily substance in 80% yield (2.56 g). IR bands (Nujol) ν: 1726 cm^{-1} (C=O), 1626 cm^{-1} (C=N), 1598 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, 3H, *J* = 6.7 Hz, $–OCH_2–\underline{C}H_3$), 2.16 (s, 3H, $H_3C–C(5)$), 2.72 (s, 3H, $–CH_3$), 4.26 (q, 2H, *J* = 6.8 Hz, $–OCH_2–CH_3$), 7.06 (d, 2H, Ar'–H), 7.28 (d, 2H, Ar'–H), 7.42–7.64 (m, 5H, Ar"–H); ^{13}C NMR ($CDCl_3$) δ: 0.96 (q, 1C, $H_3C–C(5)$), 13.58 (q, 1C, $–CH_2–\underline{C}H_3$), 21.06 (q, 3H, $H_3C–C(4')$), 59.08 (t, 1C, $–\underline{C}H_2–$), 108.44 (s, 1C), 124.04 (d, 2C), 124.44 (d, 1C), 127.66 (d, 2C), 128.58 (d, 2C), 130.18 (d, 2C), 132.52 (s, 1C), 134.86 (d, 1C), 138.32 (s, 1C), 161.02 (s, 1C), 176.16* (s, 1C, 5-C), 169.22* (s, 1C, CO). MS (relative intensity) m/e for $C_{20}H_{20}N_2O_2$: 321 (M+1, 100), 291(30), 247 (40), 232 (22), 208 (26), 164 (78), 112 (18), 91 (42), 88 (12), 29(26). Anal. Calcd: C, 74.98; H, 6.29; N, 8.74%. Found: C, 74.92; H, 6.17; N, 8.66%.

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СИНТЕЗ И АНТИМИКРОБНА АКТИВНОСТ НА ПИРАЗОЛОВИ ПРОИЗВОДНИ ПОЛУЧЕНИ ЧРЕЗ 1,3-ДИПОЛЯРНО ЦИКЛОПРИСЪЕДИНЯВАНЕ НА НИТРИЛИМИНИ И ЕТИЛАЦЕТОАЦЕТАТ

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(Резюме)

Етилацетоацетат реагира с нитрилимини получени *in situ* чрез каталитично дехидрогениране на дифенил-хидразон в присъствие на хлорамин-Т (CAT) до получаване на съответни региоселективни циклоадукти с добив 80%. Структурата на тези съединения е охарактеризирана с ИЧС, ^{1}Н ЯМР, ^{13}С ЯМР, масспектрометрия и елементен анализ. Всички пиразолови производни са изпитани за техните антибактериална и антигъбична активности.