Enaminones as Building Blocks in Organic Synthesis: a Novel Route to Polyfunctionally Substituted Benzonitriles, Pyridines, Eneylbenzotriazoles and Diazepines

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An efficient synthesis of enaminones **1a-c** is reported. Compounds **1a-c** reacted with diethyl-3-amino-2-cyanopenten-1,5-dicarboxylate (**3**) to yield the benzonitriles **6**. On the other hand, the reaction of **1a-c** with 3-amino-2-cyano-2-pentene dinitrile (**7**) afforded a mixture of benzonitriles **10** and pyridines **9**. The reaction of **1a-c** with 3-aminocrotononitrile **11** has afforded the 4-substituted-3-cyano-2-methylpyridines **15a-c**. The reaction of ethylene diamine with **1a-c** afforded 5-substituted-2,3-dihydro-1*H*-[1,4]diazepines **18a-c**. On the other hand, **1a-c** reacted with *o*-phenylenediamine to yield the 4-(2-aminopheynlamino)-substituted enaminones **21**. Compounds **21** could be converted into the benzotriazolylenones **22** on treatment with sodium nitrite in acetic acid solution.

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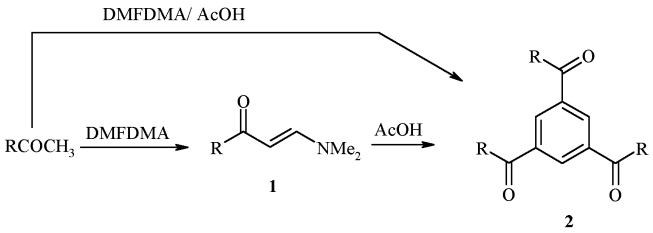
In conjunction to pervious interest in exploring synthetic potential of enaminones [1-5] we report on synthesis and reactivity of **1a-c**. Although **1a-c** has been prepared earlier from reaction of methyl ketones with DMFDMA in refluxing toluene [5] yields of **1a-c** under these conditions never exceeded 40%. Trials to adopt other literature procedure [6] of reacting methyl ketones with DMFDMA in refluxing acetic acid afforded in our hands only trimers **2a-c** which has recently been obtained on refluxing **1a-c** in AcOH [7,8]. Now we report 70-80% yield synthesis of **1a-c** *via* refluxing a mixture of methyl ketones with little excess of DMFDMA (1:1.2 mole) for six hours in absence of solvent.

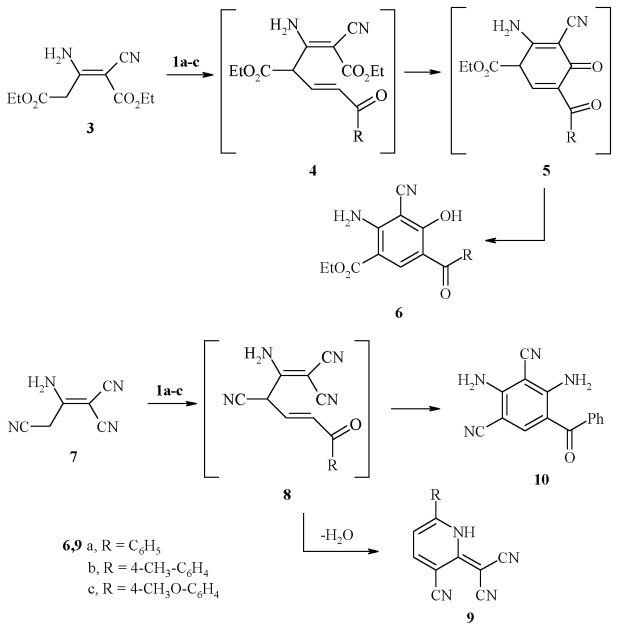


Compounds **1**, so formed reacted with diethyl 3-amino-2-cyanopenten-1,5-dicarboxylate (**3**) to yield products of condensation *via* dimethylamine elimination. These were assigned structure **6** and are assumed to be formed *via* intermediates **4** and **5**.

On the other hand, reaction of 3-amino-2-cyano-2-pentene dinitrile (**7**) with **1a** afforded a mixture of two products. These were identified as **9** and **10** based on spectral data. Compounds **9** and **10** are assumed to be formed *via* the common intermediate **8**, which either losses water to yield **9** or cyclize *via* addition of electron rich double bond in **8** to the cyano group to give **10.** But in case of **1b,1c** only compound **9** could be isolated.

The reaction of **1a-c** with 3-aminocrotononitrile **11** afforded the pyridine derivative **15** *via* the intermediates **14**, but not **12**. Although this reaction can afford **13** as

Scheme 1

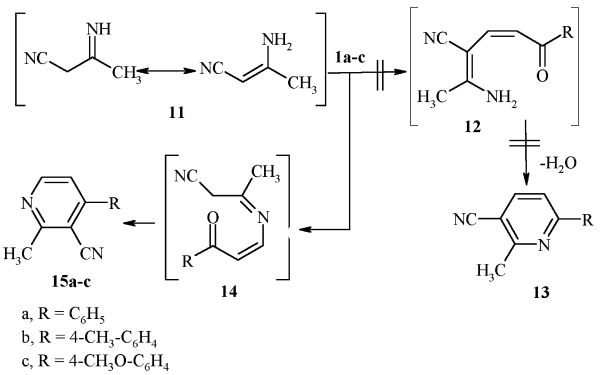


well, structure **15** is established based on H-5, 6 coupling of pyridine which showed a value of 4 Hz, if the reaction product is **13** one would expect these protons to have $J \sim 9$Hz. [9].

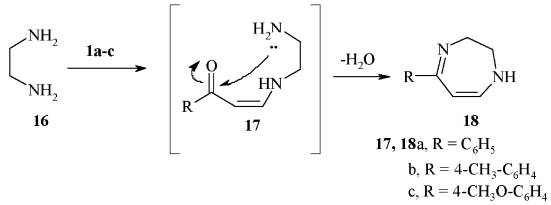
The reaction of ethylenediamine with **1a-c** in refluxing ethanol afforded the diazepene **18** *via* the nonisolable intermediate **17**.

On the other hand, the reaction of **1a-c** with *o*-phenylenediamine afforded products of condensation *via* dimethylamine elimination. These were assigned *cis* structure **21** rather than *trans* structure **20** based on ^{1}H NMR which revealed signals for *cis* olefinic protons at δ 6.04 and δ 8.40 ppm, (J = 9 Hz). The predominance of this form may be due to fixation by hydrogen bonding. Attempted cyclisation of **21** into diazepene derivatives failed under a

Scheme 2

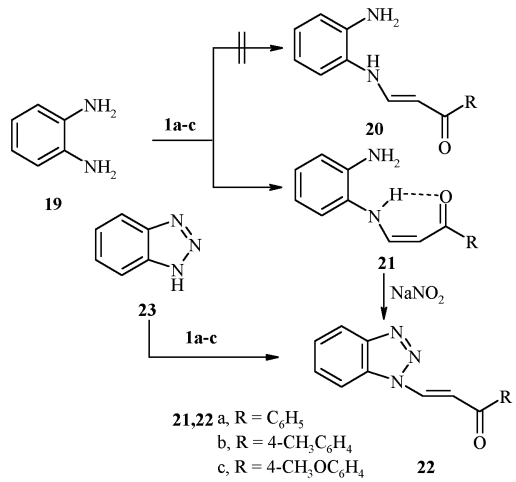


Scheme 3



Varity of conditions. However, diazotization afforded the trans enaminone **22**, which was also obtained from reaction of benzotriazole **23** with **1a-c**.

Scheme 4



EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded with FTIR-8201 PC spectrophotometer Shimadzu. ^{1}H-NMR spectra were obtained on a Varian Germini 200 MHz spectrometer in DMSO-d_6 as solvent and TMS as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP-1000 EX using the direct inlet system and EI + QI MSLMRUPLR. Microanalysis were performed by the Microanalytical Unit at Cairo University.

Ethyl 2-Amino-5-aroyl-3-cyano-4-hydroxybenzoate (**6a-c**).

A mixture of enaminone **1a-c** (0.01 mol), ethyl cyanoacetate dimer (0.01 mol) and few drops of triethylamine in 1,4-dioxan (20 ml) was refluxed for 8-12 h. After removel of the solvent, the residue was chromatographed on silica gel using EtOAc/$CHCl_3$ 4:1 as eluent.

Ethyl 2-Amino-5-benzoyl-3-cyano-4-hydroxybenzoate (**6a**).

This compound was obtained in yield (63%), mp. 205 °C; ir (KBr) νmax/cm^{-1}: 3430 (OH), 3420 (NH_2), 2985 (CH aliph), 2187 (CN), 1710 (CO, ester), 1658 (CO); ms: m/z = 310 (M^+, 13.5%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 1.34 (t, 3H, *J* = 7.5 Hz, CH_3), 4.10 (q, 2H, *J* = 7.5 Hz, CH_2), 6.03 (b, 2H, NH_2), 7.14-7.83 (m, 6H, H-Ar), 13.1 (s, 1H, OH).

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.51, N, 9.03%. Found C, 65.50; H, 4.50; N, 9.30.

Ethyl 2-Amino-3-cyano-4-hydroxy-5-(*p*-methylbenzoyl)benzoate (**6b**).

This compound was obtained in yield (58%), mp 220 °C; ir (KBr) νmax/cm^{-1}: 3450 (OH), 3422 (NH_2), 2958 (CH aliph), 2195 (CN), 1708 (CO, ester), 1645 (CO); ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 1.41 (t, 3H, *J* = 7.5 Hz, CH_3), 1.73 (s, 3H, CH_3), 4.32 (q, 2H, *J* = 7.5 Hz, CH_2), 5.93 (b, 2H, NH_2), 7.13-7.72 (m, 5H, H-Ar), 12.91 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.93, N, 8.64%. Found C, 66.60; H, 4.80; N, 8.80.

Ethyl 2-Amino-3-cyano-4-hydroxy-5-(4-methoxybenzoyl)benzoate (**6c**).

This compound was obtained in yield (53%), mp 195 °C; ir (KBr) νmax/cm^{-1}: 3465 (OH), 3435 (NH_2), 2982 (CH aliph), 2190 (CN), 1715 (CO, ester), 1638 (CO); ms: m/z = 340 (M^+, 35%). ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 1.34 (t, 3H, *J* = 7 Hz, CH_3), 3.56 (s, 3H, OCH_3), 4.41 (q, 2H, *J* = 7 Hz, CH_2), 5.83 (s, 2H, NH_2), 7.03-7.71 (m, 5H, H-Ar), 12.62 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.70, N, 8.23%. Found C, 63.50; H, 4.80; N, 8.10.

Preparation of Compounds (**9a-c**) and **10**.

General Procedure.

To a solution of enaminones **1a-c** (0.01 mol) in absolute ethanol (30 ml) and malononitrile dimer (0.01 mol) a few drops of piperidine were added. The mixture was refluxed for 7-9 h. The solvent was evaporated under reduced pressure, and the solid product so formed was collected by filtration washed several time with water dried and recrytallized from benzene in case of **9a,c** and **10** and ethanol in case of **9b**, compound **9a** and **10** were separated by fractional crystallization from benzene to afforded insoluble **10** (23%) and soluble **9** (35%) which precipitate on cooling.

2-[3-Cyano-6-phenylpyridin-2-(1*H*)-ylidene]malononitrile (**9a**).

This compound was obtained in yield (35%), mp 315 °C; ir (KBr) νmax/cm^{-1}: 3340 (NH), 2210, 2187 (3CN); ms: m/z = 244 (M^+, 100%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 7.51-7.80 (m, 5H, H-Ar), 8.31 (d, 1H, *J* = 6Hz, 4 H-pyridine), 8.63 (d, 1H, *J* = 6 Hz, 5H-pyridine), 10.72 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_8N_4$: C, 73.77; H, 3.27, N, 22.95%. Found C, 74.0; H, 3.20; N, 23.10.

2-[3-Cyano-6-(p-tolyl)pyridin-2-(1H)-ylidene]malononitrile (**9b**).

This compound was obtained in yield (55%), mp 298 °C; ir (KBr) νmax/cm^{-1}: 3330 (NH), 2989 (CH aliph), 2215, 2195 (3CN); ms: m/z = 258 (M$^+$, 100%). ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 2.41 (s, 3H, CH_3), 7.31-7.71 (m, 4H, H-Ar), 8.42 (d, 1H, *J* = 8Hz, 4H-pyridine), 8.59 (d, 1H, *J* = 8Hz, 5H-pyridine), 10.13 (b, 1H, NH)

Anal. Calcd. for $C_{16}H_{10}N_4$: C, 74.41; H, 3.87, N, 21.70%. Found C, 74.50; H, 3.60; N, 21.90.

2-[3-Cyano-6-(*p*-methoxyphenyl)pyridin-2-(1*H*)-ylidene]malononitrile (**9c**).

This compound was obtained in yield (93%), mp 315 °C; ir (KBr) νmax/cm^{-1}: 3305 (NH), 2984 (CH aliph), 2218, 2192 (3CN); ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 3.54 (s, 3H, OCH_3), 7.13-7.82 (m, 4H, H-Ar), 8.31 (d, 1H, *J* = 8Hz, 4 H-pyridine), 8.71 (d, 1H, *J* = 6 Hz, 5 H-pyridine), 10.64 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{10}N_4O$: C, 70.07; H, 3.64, N, 20.43%. Found C, 70.20; H, 3.40; N, 20.60.

6-Benzoyl-1,3-diamino- -2,4-dicyanobenzene (**10**).

This compound was obtained in yield (23%), mp 325 °C; ir (KBr) νmax/cm^{-1}: 3490, 3340, 3230 (NH_2), 2218 (2CN), 1647 (CO); ms: m/z = 262 (M$^+$, 52%), ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 6.35 (b, 2H, NH_2), 7.35-7.86 (m, 6H, H-Ar), 8.72 (b, 2H, NH_2).

Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.70; H, 3.81, N, 21.37%. Found C, 68.60; H, 3.90; N, 21.30.

4-Aryl-2-methylpyridine-3-carbonitrile (**15a-c**).

General Procedure.

A mixture of each compound **1a-c** (0.01 mol) and acetonitrile dimer 12 (0.015 mol) was refluxed in ethanol (30 ml) in presence of sodium ethoxide (0.01 mol) for 3-6 h. The solvent was removed and the residue was chromatographed on silica gel using EtOAc/petroleum ether 60-80 (3:7) as eluent. The product was crystallized from ethanol.

3-Cyano-2-methyl-4-phenylpyridine (**15a**).

This compound was obtained in yield (67%), mp 135 °C; ir (KBr) νmax/cm^{-1}: 2923 (CH aliph), 2221 (CN); ms: m/z = 194 (M$^+$, 100%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 2.84 (s, 3H, CH_3), 7.21-7.91 (m, 5H, H-Ar), 8.07 (d, 1H, *J* = 4 Hz, H-5-pyridine), 8.17 (d, 1H, *J* = 4 Hz, H-6 pyridine).

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.41; H, 5.15, N, 14.43%. Found C, 80.50; H, 5.10; N, 14.30.

3-Cyano-2-methyl-4-(p-tolyl)pyridine (**15b**).

This compound was obtained in yield (62%), mp 143 °C; ir (KBr) νmax/cm^{-1}: 2989 (CH aliph), 2218 (CN); ms: m/z = 208 (M$^+$, 100%). ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 2.21 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 7.1-7.83 (m, 4H, H-Ar), 8.03 (d, 1H, *J* = 4 Hz, H-5 pyridine), 8.06 (d, 1H, *J* = 4 Hz, H-6 pyridine).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.76; H, 5.76, N, 13.46%. Found C, 80.60; H, 5.60; N, 13.50.

3-Cyano-2-methyl-4-(*p*-methoxyphenyl)pyridine (**15c**).

This compound was obtained in yield (65%), mp 128 °C; ir (KBr) νmax/cm^{-1}: 2998 (CH aliph), 2215 (CN); ^{1}H nmr (dimethyl sulfoxide-d_6): δ (ppm) = 2.83 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 7.35-7.89 (m, 4 H, H-Ar), 8.04 (d, 1H, *J* = 4 Hz, H-5 pyridine), 8.08 (d, 1H, *J* = 4 Hz, H-6 pyridine).

Anal. Calcd. for $C_{14}H_{12}N_2O$ C, 75.0; H, 5.35, N, 12.50%. Found C, 75.0; H, 5.40; N, 12.60.

Preparation of compounds (**18a-c**) and (**21a-c**).

General Procedure.

A mixture of enaminones **1a-c** (0.01 mol) and ethylene diamine or *o*-phenylene diamine (0.01 mol) in absolute ethanol (30 ml) was refluxed for 5-8 h. The solvent was partially removed and the solid product so formed was collected on cooling and recrytallized from ethanol.

5-Phenyl-1,2,3-trihydro[1,4]diazepine (**18a**).

This compound was obtained in yield (85%), mp 192 °C; ir (KBr) νmax/cm^{-1}: 3310 (NH), 2985 (CH aliph); ms: m/z = 172 (M$^+$, 86%); ^{1}H nmr (deuteriochloroform): δ (ppm) = 3.34 (t, 4H, *J* = 6.4, $2CH_2$), 5.7 (d, 1H, *J* = 8 Hz, H-6), 6.73 (d, 1H, *J* = 8 Hz, H-7), 7.15-7.75 (m, 5H, H-Ar), 10.46 (b, 1H, NH).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.74; H, 6.97, N, 16.27%. Found C, 76.70; H, 6.90; N, 16.30.

5-(*p*-Tolyl)-1,2,3-trihydro[1,4]diazepine (**18b**).

This compound was obtained in yield (80%), mp 200 °C; ir (KBr) νmax/cm^{-1}: 3340 (NH), 2985 (CH aliph); ms: m/z = 186 (M$^+$, 38%); ^{1}H nmr (deuteriochloroform): δ (ppm) = 2.38 (s, 3H, CH_3), 3.42 (t, 4H, *J* = 6.4 Hz, CH_2), 5.6 (d, 1H, *J* = 8 Hz, H-6), 6.80 (d, 1H, *J* = 8 Hz, H-7), 7.23 (d, 2H, *J* = 8 Hz, H-Ar), 7.46 (d, 2H, *J* = 8 Hz, H-Ar), 10.36 (b, 1H, NH).

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.41; H, 7.52, N, 15.05%. Found C, 77.50; H, 7.40; N, 15.10.

5-(p-Methoxyphenyl)-1,2,3-trihydro[1,4]diazepine (**18c**).

This compound was obtained in yield (82%), mp 183 °C; ir (KBr) νmax/cm^{-1}: 3339 (NH), 2985 (CH aliph); ms: m/z = 202 (M$^+$, 53%). ^{1}H nmr (deuteriochloroform): δ = 3.46 (d, 4H, $2CH_2$), 3.80 (s, 3H, OCH_3), 5.83 (d, 1H, *J* = 8 Hz, H-6), 6.83 (d, 1H, *J* = 6 Hz, H-7), 7.19 (d, 2H, *J* = 8 Hz, H-Ar), 7.93 (d, 2H, *J* = 8 Hz, H-Ar), 10.32 (b, 1H, NH).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.28; H, 6.93, N, 13.86%. Found C, 71.40; H, 7.10; N, 13.80.

(*Z*)-3-(2-Aminoanilino)-1-phenylprop-2-en-1-one (**21a**).

This compound was obtained in yield (78%), mp 145 °C; ir (KBr) νmax/cm^{-1}: 3450, 3320 (NH_2, NH), 2985 (CH aliph), 1640 (CO); ms: m/z = 238 (M$^+$, 65%); ^{1}H NMR (deuteriochloroform): δ = 3.77 (d, 2H, NH_2 exchangable), 6.04 (d, 1H, *J* = 9 Hz, CH-vinyl), 6.62-7.72 (m, 9H, H-Ar), 8.2 (d, 1H, *J* = 9 Hz, CH-vinyl), 12.13 (b, 1H, NH exchangeable).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88, N, 11.76%. Found C, 75.60; H, 5.80; N, 11.80.

(*Z*)-3-(2-Aminoanilino)-1-(*p*-tolyl)prop-2-en-1-one (**21b**).

This compound was obtained in yield (80%), mp 205 °C; ir (KBr) νmax/cm^{-1}: 4450, 3340 (NH_2, NH), 2985 (CH aliph), 1638 (CO); ms: m/z = 252 (M$^+$, 43%); ^{1}H NMR (deuteriochloroform): δ = 2.42 (s, 3H, CH_3), 3.77 (s, 2H, NH_2 exchangable), 6.04 (d, 1H, *J* = 9 Hz, CH-vinyl), 6.79-7.89 (m, 8H, H-Ar), 8.17 (d, 1H, *J* = 9 Hz, CH-vinyl),, 12.19 (b, 1H, NH exchangeable).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.34, N, 11.11%. Found C, 76.20; H, 7.20; N, 11.20.

(*Z*)-3-(2-Aminoanilino)-1-(*p*-methoxyphenyl)prop-2-en-1-one (**21c**).

This compound was obtained in yield (78%), mp 185-186 °C; ir (KBr) νmax/cm^{-1}: 4460, 3340 (NH_2, NH), 2995 (CH aliph), 1641 (CO); ms: m/z = 268 (M^+, 38%); ^{1}H nmr (deuteriochloroform): δ = 3.54 (s, 3H, OCH_3), 3.75 (s, 2H, NH_2 exchangable), 6.10 (d, 1H, *J* = 9 Hz, CH-vinyl), 6.78-7.94 (m, 8H, H-Ar), 8.4 (d, 1H, *J* = 9 Hz, CH-vinyl), 12.30 (b, 1H, NH exchangeable).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97, N, 10.44%. Found C, 71.60; H, 5.90; N, 10.50.

Preparation of (*E*)-1-Aryl-3-(1H-1,2,3-benzotriazol-1-yl)-prop-2-en-1-one **22a-c**.

General Procedure.

Method A:

A solution of glacial acetic acid (10 ml) was added dropwise to a stirred suspension of **22a-c** (0.01 mol) and sodium nitrite (0.015 mol) in water (2 ml) at room temperature for 3 h, the precipitate was collected by filtration and recrystallized from ethanol.

Method B:

The same experimental described above for preparation **18a-c** by using benzotriazole (0.01 mole) instead of ethylene diamine. The solid formed crystallized from ethanol.

(*E*)-3-(1*H*-1,2,3-Benzotriazol-1-yl)-1-phenylprop-2-en-1-one (**22a**).

This compound was obtained in yield (53%), mp 134 °C; ir (KBr) νmax/cm^{-1}: 2989 (CH aliph), 1649 (CO); ms: m/z = 249 (M^+, 10%); ^{1}H nmr (deuteriochloroform): δ = 7.12-7.83 (m, 10H, H-Ar, vinyl-H), 8.51 (d, 1H, *J* = 9 Hz, CH-vinyl).

Anal. Calcd. for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.41, N, 16.86%. Found C, 72.30; H, 4.50; N, 16.70.

(*E*)-3-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(*p*-tolyl)prop-2-en-1-one (**22b**).

This compound was obtained in yield (56%), mp 122 °C; ir (KBr) νmax/cm^{-1}: 2985 (CH aliph), 1648 (CO); ms: m/z = 263 (M^+, 38%); ^{1}H nmr (deuteriochloroform): δ = 2.31 (s, 3H, CH_3), 7.12-7.78 (m, 9H, H-Ar, vinyl-H), 8.62 (d, 1H, *J* = 9 Hz, CH-vinyl)

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 73.00; H, 4.94, N, 15.96%. Found C, 73.10; H, 4.90; N, 15.90.

(*E*)-3-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(*p*-methoxyphenyl)prop-2-en-1-one (**22c**).

This compound was obtained in yield (63%), mp 143 °C; ir (KBr) νmax/cm^{-1}: 2983 (CH aliph), 1650 (CO); ms: m/z = 279 (M^+, 25%); ^{1}H nmr (deuteriochloroform): δ = 3.56 (s, 3H, OCH_3), 7.10-7.81 (m, 9H, H-Ar, vinyl-H), 8.93 (d, 1H, *J* = 9 Hz, CH-vinyl).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.65, N, 15.05%. Found C, 68.80; H, 4.70; N, 15.10.

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