An Efficient One Pot Synthesis of New Indanopyrazoline and Indanopyrazole Derivatives

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Abstract: Synthesis of a series of novel fused pyrazolines and pyrazoles has been accomplished in good yields by regio- and diastereoselective 1,3-dipolar cycloaddition of enamines of indan-1-one **1a-c** towards *C*-aryl-*N*-phenylnitrilimines **2d-f**. The structure of the cycloadducts was elucidated by 1D and 2D NMR studies.

Keywords: 1-Aminoindenes, *C*-aryl-*N*-phenylnitrilimines, [3+2] Cycloaddition, pyrazole, pyrazoline, regiochemistry.

INTRODUCTION

Pyrazolines and pyrazoles represent important nitrogen-containing five membered heterocyclic compounds and various methods have been worked out for their synthesis [1-4]. Derivatives of pyrazolines and pyrazoles have played a crucial role in the history of heterocyclic chemistry and have been used extensively as important pharmacophores and synthons in the field of organic chemistry and drug design.

Several pyrazoline derivatives have been found to process considerable activity such as antifungal [5], antidepressant [6-9] anticonvulsant [8, 9], anti-inflammatory [10], antibacterial [11] and anti-tumor [12] properties. Moreover, many selectively fluoro-substituted organic compounds show peculiar pharmacological and agrochemical properties [13-18].

2-pyrazoline seems to be one the most frequently studied derivatives among all pyrazoline-type compounds. Pyrazoles are extensively used in the field of medicine and agrochemistry. A number of pyrazole derivatives have been reported to process interesting biological activities like anti-inflammatory, antimicrobial, antiprotozoal and cerebro-protective [19-22].

Several methods are employed for the synthesis of pyrazolines, including the condensation of chalcones with hydrazine, hydrazine derivatives [23-27] and thiosemi-carbazide [28] under acidic [23, 24] or basic [28] conditions, and the cycloaddition of nitrilimines with carbon-carbon double bonds of a suitable dipolarophile [29-32].

Pyrazoles can be easily prepared from nitrilimines and dipolarophiles bearing a carbon-carbon double or triple bonds in a two-step reaction, the subsequent oxidative heteroaromatization of pyrazolines requires drastic reaction conditions.

Since several years, we have focused our research on the reactivity of dipolarophiles bearing an exo- and endocyclic carbon-carbon double bond towards several 1,3-dipole such as nitrile oxides [33], diazoalkanes [34] and diarylnitrilimines [35].

In continuation of our work in the area of cycloaddition reactions, we report herein on the efficient synthesis of series of novel fused pyrazolines and pyrazoles by regio- and stereoselective 1,3-dipolar cycloaddition of enamines of indan-1-one **1a-c** towards *C*-aryl-*N*-phenylnitrilimines **2d-f**.

In our previous work, we have reported the 1,3-dipolar cycloaddition of diphenylnitrilimine with enamines of 1-tetralone at benzene reflux [36]. Under these conditions, only the pyrazoles were isolated, resulting from the loss of the amino group in the acidic reaction medium from the intermediate pyrazolines. In a preliminary note, some members of our group have already reported the reaction of C-*p*-anisyl-*N*-phenylnitrilimine towards 3,3-dimethylindan-1-one at benzene reflux [37]. For the first time, we have now succeeded to isolate and to characterize the pyrazolines **3** bearing a cyclic amino-substituent. The later were obtained as the major products from reaction conducted in toluene at 60° C instead of refluxing benzene, implementing the [3+2] cycloaddition of *C*-aryl-*N*-phenylnitrilimines towards enamines of indan-1-one.

The results reported herein were aimed at the preparation of some new pyrazolines and pyrazoles derivatives with anticipated biological activities.

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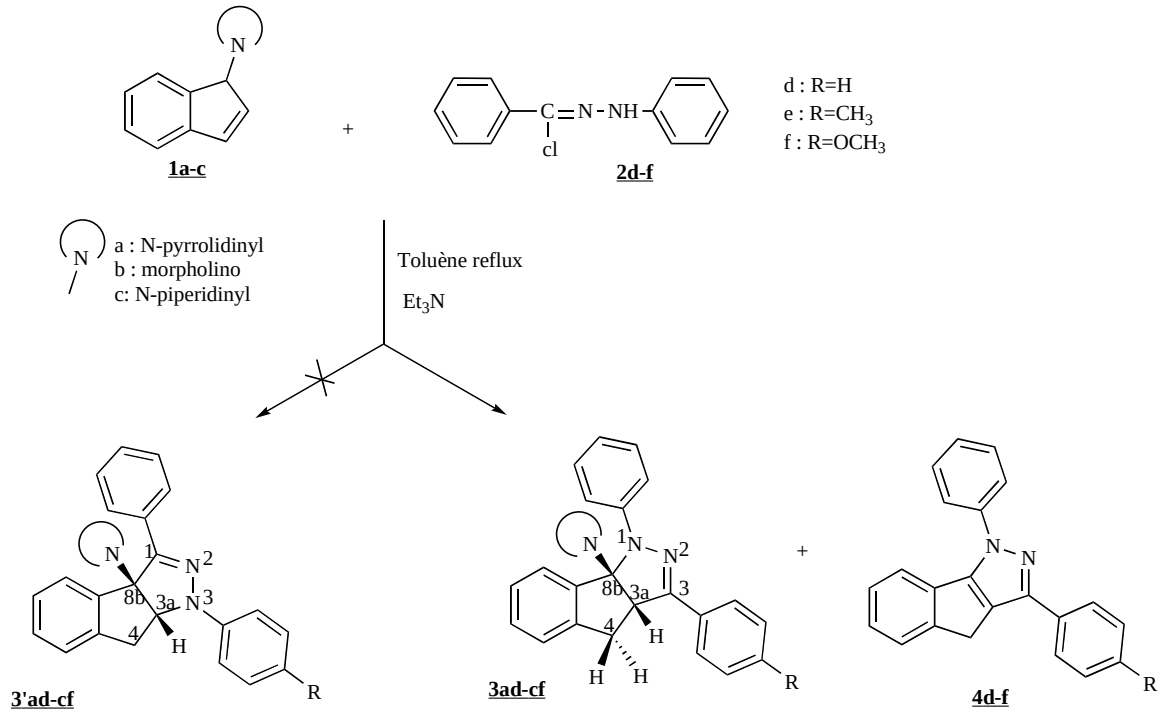
RESULTS AND DISCUSSION

In order to evaluate the effect of an electron-donating group on the double bond, the cycloaddition of *C*-aryl-*N*-phenylnitrilimine **2d-f** (generated *in situ* by the dehydrochlorination of hydrazonoyl chlorides with triethylamine) with various enamines of indan-1-one **1a-c** was carried out at 60°C in toluene (Scheme **1**). This choice was based on previous results [36, 37] which show that a secondary amino group is very essential leaving group in [3+2] cycloaddition. The reaction leads to a mixture of two products, the 4*H*-3a,8b-dihydro-indeno[2,3-*d*]pyrazolines **3ad-cf (**45-60 %) and the derivatives 4*H*-indeno[2, 3-d]pyrazoles **4** (30-38 %, see Table **1**).

These products were isolated by column chromatography, using hexane/ ethyl acetate as an eluent. Unfortunately, we failed in obtaining suitable crystals of cycloadducts **3** and pyrazoles **4** for an X-ray analysis. The assigned structures **3ad-cf** and **4** are, however, unambiguously supported by analytical and spectroscopic data (IR, ^{1}H, ^{13}C NMR, see experimental part).

The 1,3 dipolar cycloaddition of *C*-aryl-*N*-phenylnitrilimines is in each case 100% regioselective. The regioselectivity of the adducts **3ad-cf** was accessed by ^{1}H and ^{13}C NMR spectroscopy. The ^{13}C NMR studies gave a singlet for the quaternary carbon C-8b at 96 ppm. On the other side, a doublet was observed for the tertiary carbon C-3a at around 44.33-49.93 ppm ($CDCl_3$/TMS). The ^{1}H NMR spectra (300 MHz) exhibit a doublet of doublets between 3.8 ppm and 4 ppm attributed to the 3a-H proton. Note that in the case of the reverse regioisomers **3'**, one should observe a chemical shift value higher than 4.9 ppm for the 3a-H proton [36, 38]. The 1,3-dipole can be oriented by a secondary



Scheme 1. Reactions of amino-indenes **1a-c** with C-aryl-N-phenylnitrilimines **2d-f**.

Table 1. Yields of 4*H*-3a,8b-dihydro-indeno[2, 3-*d*]pyrazoline 3ad-cf and 4*H*-indeno[2, 3-*d*]pyrazoles 4df

Entry	Dipolarophiles	Dipoles	Pyrazolines[a]	Yield[b](%)	Pyrazoles	Yield(%)
1	a	d	**3ad**	54	**4d**	37
	a	e	**3ae**	50	**4e**	34
	a	f	**3af**	60	**4f**	35
2	b	d	**3bd**	45	**4d**	35
	b	e	**3be**	50	**4e**	36
	b	f	**3bf**	55	**4f**	31
3	c	d	**3cd**	51	**4d**	38
	c	e	**3ce**	50	**4e**	34
	c	f	**3cf**	55	**4f**	30

[a]Reaction in toluene at 60°C during 3 days.

amino group fixed on the C-atom of the dipolarophilic double bond. In any case, the terminal nitrogen atom of the dipole is linked with the C-atom bearing the amino group. The chemical shifts of their 3a-H proton corresponded to those of 3a-H of the related pyrazolines derivatives obtained in our previous work from *C*-*p*-anisyl-*N*-phenylnitrilimine towards 3,3-dimethylindan-1-one [37]

Further confirmation for the proposed regiochemistry is provided from the HMBC spectra, which show two correlations between 4-H, 4'-H with C-3 at 160 ppm and 4-H, 4'H with C-3' at 139 ppm: (Fig. **1**). This excludes the presence of the inverse regioisomer **3'**, in which the last correlations should be absent (4-H and 4'-H present a ^5J coupling constant with C-3').

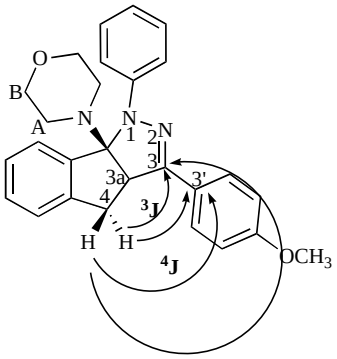


Fig. (1). selected HMBC correlations of **3bf**.

For all pyrazolines **3** the chemical shifts of each hydrogen atom attached on a sp^3 carbon atom, have been unambiguously attributed according to the observations made in previous reports [39-41]. Indeed, it was clearly established that the values of *cis* coupling constants were always larger than that of the *trans* coupling constants. Furthermore, the *J* value of 4.2 Hz suggests that the protons at 3.35 ppm (4'-H), are in *trans* relationship with that at 3.80 ppm (3a-H). The doublets of doublets at 3.62- 3.75 ppm are assigned to 4-H in *cis* relationship with 3a-H due to the *J* values of 7.8 or 9.3 Hz. In addition, it has been shown that the difference in chemical shifts of the two C-4 protons, with *J* coupling constants of 12.9 - 13.8 Hz in *gem*-position can be used to establish the relative stereochemistry of the C-3a and C-4.

The acid-catalyzed transformation of compound **3** produces more stable heteroaromatic pyrazoles derivatives **4**. This result can be explained by the presence of an excess of hydrogen chloride, liberated from *C*-aryl-*N*-phenylbenzohydrazidochloride; which promotes then the elimination of amino group.

In order to verify, whether product **4** stems from **3,** we first refluxed compound **3** in a EtOH/HCl 12 M mixture (10:1) (Scheme **2**). The physical characteristics, IR and NMR spectroscopic data of the isolated products **4d-f** were identical to those of compounds **4** generated initially in the *in situ* one-pot reaction. It is interesting to note that independent of the nature of the amino group of the enamines, cycloaddition leads to the same result. The reactions were carried out with pyrolydinyl, morpholino and piperidinyl groups.

MATERIALS AND METHODS

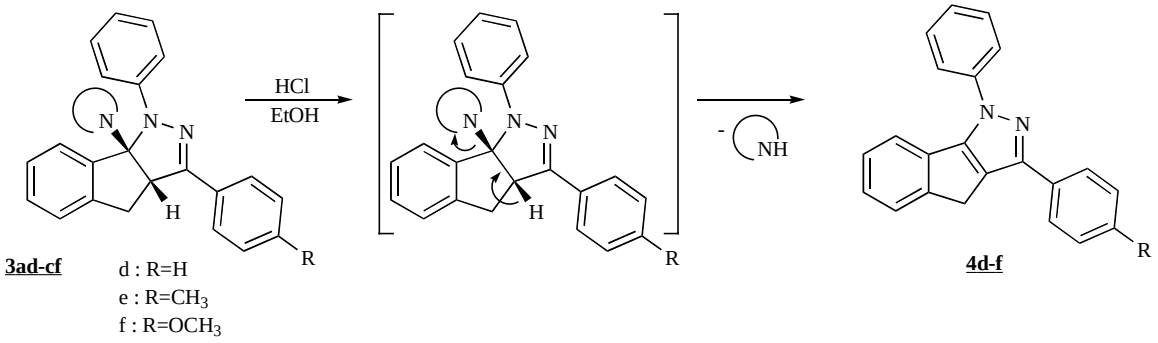
Reactions were carried out under an atmosphere of dry N_2. Solvents were purified by standard methods and freshly distilled under nitrogen and dried before use. Melting points were determined on a Kofler bank. Only structurally significant bands are reported. NMR spectra were recorded on a Bruker-Spectrospin AC 300 spectrometer operating at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C. Chemical shifts were measured relative to TMS in $CDCl_3$ as a solvent. Materials: thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm 200×200 nm).

The enamines of indan-1-one **1a-c** were prepared by reacting given secondary amine with indanone, often in the presence of an acid catalyst according to reported methods [42-44].

The *C*-aryl-*N*-phenylnitrilimines were prepared *in situ* from the respective hydrazonoyl chlorides **2d-f** by reaction with triethylamine according to ref [45, 46].

General Procedure for the Preparation of the Cycloadducts 3ad-cf and 4d-f

A magnetically stirred solution of dipolarophiles **1a-c** and *C*-aryl-*N*-phenylnitrilimines **2d-f** in dry toluene, was kept at 60°C for 3 days. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate mixture (80/20) as eluent to afford compounds **3ad-cf and 4d-f**.



Scheme 2. Formation of pyrazoles **4d-f** by elimination of amino group.

1,3-diphenyl-8b-pyrolydinyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3ad)

Yield (54%); green needles; Mp 172 °C; **IR** (KBr): ν 1583, 1248 cm^{-1}; **^{1}H NMR** ($CDCl_3$) :δ 1.10-1.15 (m, 4H); 3.36 (dd, 1H, *J*=4.2Hz, *J*=12.9Hz); 3.5-3.61 (m, 4H); 3.72 (dd, 1H, *J*=9.3Hz, *J*=12.9Hz); 3.79 (dd, 1H, *J*=4.2Hz, *J*=9.3Hz); 6.88-7.83 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$) : δ 24.28 (C_A) ; 30.14 (C-4); 47.52 (N-C); 49.52 (C-3a); 96 (C-8b) ;158.71(C-3); 112.77-166.50 (aromatic C). Anal. Calcd. for $C_{26}H_{25}N_3$: C 82.29%, H 6.64%, N 11.07%. Found: C 82.41%, H 6.48%, N 10.98.

3-(4-methylphenyl)-1-phenyl-8b-pyrolydinyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3ae)

Yield (50%); green needles; Mp 168 °C; **IR** (KBr): ν 1588, 1250 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.09-1.16 (m, 4H); 2.41 (s, C<u>H</u>$_3$); 3.35 (dd, 1H, *J*=4.2Hz, *J*=12.9) ; 3.55-3.59 (m, 4H); 3.62 (dd, 1H, *J*=9.3Hz, *J*=12.9Hz); 3.81(dd, 1H, *J*=4.2Hz, *J*=9.3Hz); 6.89-7.84 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 21.39 (<u>C</u>H$_3$); 24.63 (C_A); 30.18 (C-4); 47.85 (N-C); 49.93 (C-3a); 96(C-8b); 159.02 (C-3) ;113.62-167.40 (aromatic C). Anal. Calcd. for $C_{27}H_{27}N_3$: C 82.41%, H 6.92%, N 10.68%. Found: C 82.18%, H 6.84%, N 10.79.

3-(4-methoxyphenyl)-1-phenyl-8b-pyrolydinyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3af)

Yield (60%); green solid; Mp 198 °C; **IR** (KBr): ν 1595, 1254 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.13-1.16 (m, 4H); 2.41 (s, C<u>H</u>$_3$); 3.36 (dd, 1H, *J*=4.2Hz, *J*=12.9Hz); 3.50-3.61 (m, 4H); 3.69 (dd, 1H, *J*=9.3Hz, *J*=12.9Hz); 3.81(dd, 1H, *J*=4.2Hz, *J*=9.3Hz); 3.77 (s,OC<u>H</u>$_3$) 6.89-7.83 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 24.43(C_A); 30.44 (C-4); 47.43 (N-C); 49.49(C-3a); 55.70 (O<u>C</u>H$_3$); 96 (C-8b); 161.78 (C-3); 114.62-166.40 (aromatic C). Anal. Calcd. for $C_{27}H_{27}N_3O$: C 79.19%, H 6.65%, N 10.26%. Found: C 79.40%, H 6.47%, N 10.03%.

1,3-diphenyl-8b-morpholino-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3bd)

Yield (45 %); Light yellow needles; Mp 175 °C; **IR** (KBr): ν 1588, 1250 cm^{-1}; **^{1}H NMR** (CDCl3): δ 2.1-2.4 (m, 4H); 3.25-3.6 (m,4H); 3.36 (dd, 1H, J=4.2Hz, J=13.8Hz); 3.65 (dd, 1H, J=7.8Hz, J=13.8Hz); 3.80 (dd, 1H, J=4.2Hz, J=7.8Hz) 6.69- 7.49 (m, aromatic H) ppm; **NMR** ($CDCl_3$): δ 30.54 (C-4); 44.33 (C-3a); 46.86 (N-C); 66.62 (O-C); 96 (C-8b); 113.22-168.34 (aromatic C). Anal. Calcd. for $C_{26}H_{25}N_3O$: C 78.96%, H 6.37%, N 10.26%. Found: C 78.77%, H 6.25%, N 10.35%.

3-(4-methylphenyl)-8b-morpholino-1-phenyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3be)

Yield (50 %); yellow needles ; Mp 18 0 °C; **IR** (KBr): ν 1610, 1248 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.88-2.36 (m, 4H); 2.40 (s, C<u>H</u>$_3$); 3.35 (dd, 1H, *J*=4.2Hz, *J*=13.8Hz); 3.65-3.72 (m, 4H); 3.69 (dd, 1H, *J*=7.8Hz, *J*=13.8Hz); 3.88 (dd, 1H, *J*=4.2Hz, *J*=7.8Hz); 6.68-8.13 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 21.81 (<u>C</u>H$_3$); 30.56 (C-4); 44.33 (C-3a); 46.86 (N-C); 66.62 (O-C); 96 (C-8b); 112.88-167.99 (aromatic C). Anal. Calcd. for $C_{27}H_{27}N_3O$: C 79.96%, H 6.65%, N 10.26%. Found: C 80.15%, H 6.48%, N 10.19%.

3-(4-methoxyphenyl)-8b-morpholino-1-phenyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3bf)

Yield (55%); dark yellow needles; Mp 192°C; **IR** (KBr): ν 1595, 1250 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 2.63-2.65 (m, 4H); 3.05-3.10 (m, 4H); 3.40 (dd, 1H, *J*=4.2Hz, *J*=13.8Hz); 3.75 (dd, 1H, *J*=7.8Hz, *J*=13.8Hz); 3.82 (s, OC<u>H</u>$_3$); 3.80 (dd, 1H *J*=4.2Hz, *J*=7.8Hz); 6.95-7.90 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): 30.08 (C-4); 45.27 (C-3a); 47.33 (N-C); 55.65 (O<u>C</u>H$_3$); 66.97 (O-C); 96 (C-8b); 113.19-167.93 (aromatic C). Anal. Calcd. for $C_{27}H_{27}N_3O_2$: C 76.21%, H 6.40%, N 9.87%. Found: C 76.40%, H 6.41%, N 9.85%.

1,3-diphenyl-8b-piperidinyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3cd)

Yield (51%); green solid; Mp 176°C; **IR** (KBr): ν 1590, 1248 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.55 (m, 2H); 1.56 (m,4H); 2.30-2.60 (m, 4H); 3.32 (dd, 1H, *J*=4.2Hz, *J*=13.8Hz); 3.68 (dd, 1H, *J*=9.3Hz, *J*=13.8Hz); 3.80 (dd, 1H, *J*=4.2Hz, *J*=7.8Hz); 6.70-7.80 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 24.83 (C_B); 25.78 (C_A); 30.19 (C-4); 47.43 (N-C); 47.88 (C-3a); 96 (C-8b); 112.82-167.40 (aromatic C). Anal. Calcd. for $C_{27}H_{27}N_3$: C 82. 41%, H 6.92%, N 10.68%. Found: C 82.24%, H 6.95%, N 10.73%.

3-(4-methylphenyl)-1-phenyl-8b-piperidinyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3ce)

Yield (50%); green needles; Mp 165°C; **IR** (KBr): ν 1600, 1250 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.41 (m, 2H); 1.68 (m, 4H); 2.40-2.60 (m, 4H); 2.4 (s, C<u>H</u>$_3$) ; 3.35 (dd, 1H, J=4.2Hz, *J*=13.8Hz); 3.75 (dd, 1H, *J*=9.3Hz, *J*=13.8Hz); 3.80(dd, 1H *J*=4.2Hz, *J*=9.3Hz); 6.68-8.1 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 21.85 (CH_3); 25.05 (C_B); 25.94 (C_A); 30.35 (C-4);45.01 (C-3a); 47.91 (N-C); 96 (C-8b); 112.82-167.40 (aromatic C). Anal. Calcd. for $C_{28}H_{29}N_3$: C 82.52%, H 7.17%, N 10.31%. Found: C 82.29%, H 7.21%, N 10.27%.

3-(4-methoxyphenyl)-1-phenyl-8b-piperidinyl-4H-3a,8b-dihydro-indeno[2,3-d]pyrazoline (3cf)

Yield (55%); green needles; Mp 190 °C; **IR** (KBr): ν 1610, 1249 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.40 (m, 2H); 1.57 (m, 4H); 2.30-2.60 (m, 4H); 3.34 (dd, 1H, *J*=4.2Hz, *J*=13.8Hz); 3.65 (dd, 1H, *J*=9.3Hz, *J*=13.8Hz); 3.80 (dd, 1H, *J*=4.2Hz, *J*=9.3Hz); 3.82 (s, OC<u>H</u>$_3$); 6.81-7.82 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 25.08 (C_B); 25.98 (C_A); 30.28 (C-4); 46.91(N-C); 47.91(C-3a); 55.78 (O<u>C</u>H$_3$); 96 (C-8b); 113.62-165.46 (aromatic C). Anal. Calcd. for $C_{28}H_{29}N_3O$: C79.40%, H 6.90%, N 9.92%. Found: C 79.31%, H 6.99%, N 9.89%.

1,3-diphenyl-4H-indeno[2, 3-d]pyrazole (4d)

Yield (37 %); green needles; Mp 170 °C; **IR** (KBr): ν 1595, 1248 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.74 (s, H_4); 6.72-7.90 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 30.15 (C-4); 112-149 (aromatic C). Anal. Calcd for $C_{22}H_{16}N_2$: C 85.69%, H 5.23%, N 9.08%. Found: C 85.97%, H 5.01%, N 9.13%.

3-(4-methylphenyl)-1-phenyl-4H-indeno[2, 3-d]pyrazole (4e)

Yield (34 %); yellow needles; Mp 180°C; **IR** (KBr): ν 1600, 1237 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 2.45 (s, CH_3); 3.88 (s,

H_4); 7.26-7.90 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 21.45 (CH_3); δ 30.20 (C-4); 119.51-149.38 (aromatic C). Anal. Calcd. for $C_{23}H_{18}N_2$: C 85.68%, H 5.63%, N 8.69%. Found: C 85.19%, H 5.69%, N 8.71%.

3-(4-methoxyphenyl)-1-phenyl-4H-indeno[2, 3-d]pyrazole (4f)

Yield (35 %); yellow needles; Mp 191 °C; **IR** (KBr): ν 1620, 1250 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.79 (s, $OC\underline{H}_3$); 3.76 (s, H_4); 6.91-7.85 (m, aromatic H) ppm; **^{13}C NMR** ($CDCl_3$): δ 30.08 (C-4); δ 55.72 ($O\underline{C}H_3$); 114.51-159.88 (aromatic C). Anal. Calcd. for $C_{23}H_{18}N_2O$: C 81.63%, H 5.36%, N 8.28%. Found: C 81.86%, H 5.34%, N 8.33%.

CONCLUSION

In conclusion, we have shown that cycloaddition reaction of enamines of indan-1-one **1a-c** with *C*-aryl-*N*-phenylnitrilimines **2d-f** leads regioselectively and respectively to a mixture of the 4*H*-3a,8b-dihydro-indeno[2, 3-*d*]pyrazoline **3ad-cf** and 4*H*-indeno[2, 3-d]pyrazoles **4d-f**.

The great interest in *C*-aryl-*N*-phenylnitrilimines reactions on enamines of indan-1-one lies in the fact that it is possible to obtain in high regioselectivity and directly the pyrazolines derivatives. Independently, the conversion of the pyrazolines **3** in acidic medium leads to the same pyrazole **4** as those formed *in situ* in the one-pot reaction.

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