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A FACILE ACCESS AND COMPUTATIONAL STUDIES OF SOME NEW 4,5'-BIPYRAZOLE DERIVATIVES

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Abstract – 4,5'-Bipyrazoline-5-carboxylate ester **4** was regioselectively obtained from 1,3-dipolar cycloaddition reaction of nitrilimine **2** with ethyl 2-cyano-5-phenylpenta-2,4-dienoate (**3**). The bipyrazoline-5-carboxylate ester **4** underwent thermal elimination of hydrogen cyanide upon heating in DMF to afford bipyrazole **10**. Heating the 4,5'-bipyrazole derivative **4** in ethanolic sodium ethoxide solution afforded the bipyrazole **11** via concurrent decarboxylation and hydrogen cyanide elimination. Oxidation of the latter product with tetrachloro-1,4-benzoquinone gave the 4,5'-bipyrazole **12**. The regioselectivity of the reaction was studied in the light of some theoretical reactivity indices and the frontier molecular orbital (FMO) theory using the B3PW91/6-31G(d) level of calculation as well as some thermodynamic properties using the PM6 semi-empirical level of calculation. The analysis of the data obtained reveals that the dipolar cycloaddition reactions in the present study can be classified in the normal electron demand category.

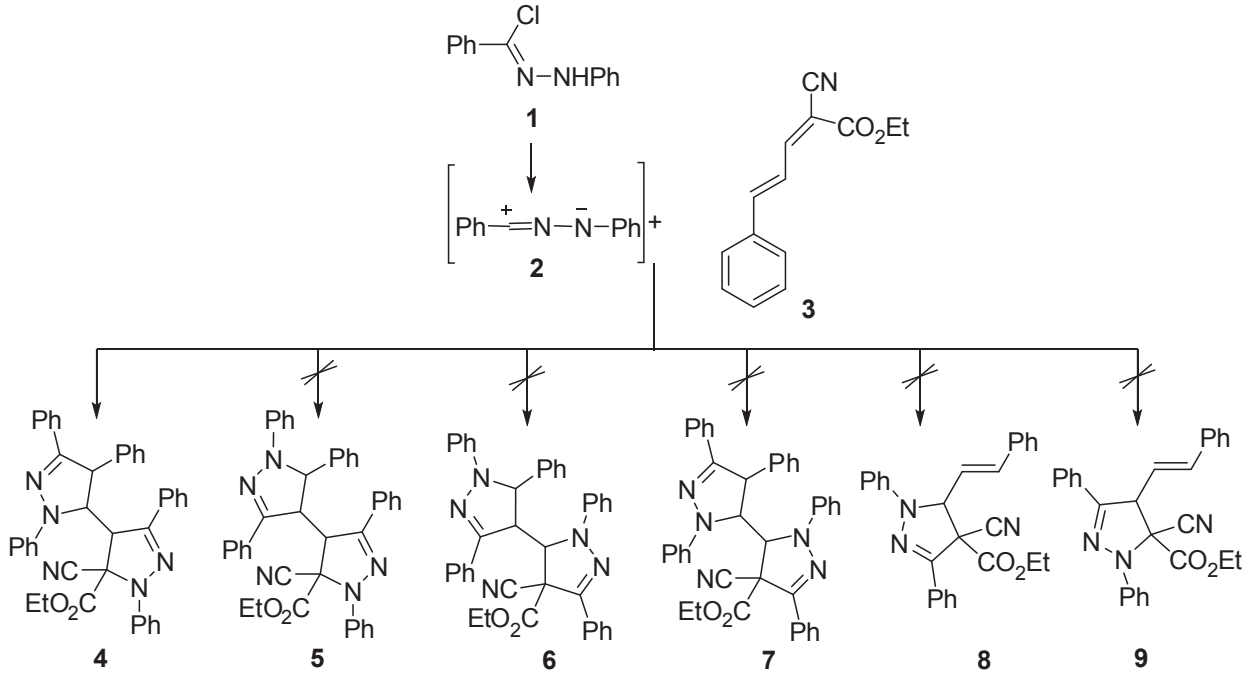
INTRODUCTION

Bipyrazole derivatives represent an interesting class of heterocycles which are reported as pharmacologically important compounds with an array of biological activities.[1] Most of the pharmacologically active bipyrazole derivatives are useful as potent antibacterial,[2] anti-inflammatory,[3-5]

cytotoxic agents,[6,7] insecticides,[8] herbicides[9] and fungicides.[10] Bipyrazoles are also being used as corrosion inhibitors of steel[11,12] and in the synthesis of heat resistant polymers.[13] In continuation of our research program directed towards the synthesis of a variety of bipyrazole ring systems of potential biological activities,[14-20] we report in this communication a regioselective synthesis of some new 4,5'-bipyrazole derivatives *via* 1,3-dipolar cycloaddition reaction of the nitrilimine **2** with ethyl 2-cyano-5-phenylpenta-2,4-dienoate (**3**).

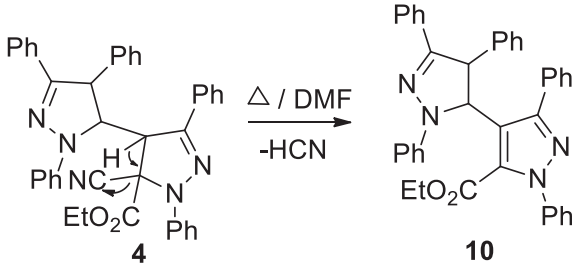
RESULTS AND DISCUSSION

Treatment of an equimolar ratio of ethyl (2*Z*,4*E*)-2-cyano-5-phenyl-2,4-pentadienoate (**3**)[21] with the nitrilimine **2** (generated in situ from *N*'-phenylbenzohydrazonoyl chloride (**1**)[22] by the action of triethylamine in benzene at room temperature) afforded only one product, as examined by TLC. Spectral data and elemental analyses revealed that the product is 1:2 instead of the expected 1:1 cycloadduct. When the above reaction between **2** and **3** was repeated in 1:2 molar ratio under typical reaction condition, only one 1:2 cycloadduct was obtained but in higher yield. Therefore, regardless of the molar ratio of the reactants, the product was the same every time. The structure of the isolated product was identified as 4,5'-bipyrazole derivative **4** (Scheme 1). The distinction between the four possible 1:2 regioisomeric cycloadducts was made on the basis of spectral data on the isolated product. Although cycloadduct **4** or **5** has a nitrile function, its IR revealed the absence of nitrile absorption band similar to the case of aliphatic nitriles activated by an oxygen or nitrogen atom at the α-position.[23,24] The absence of the nitrile absorption in the IR spectra excludes also the possibility of formation of the other regioisomers **6** or **7**. Moreover, the ^{1}H NMR spectrum of the formed cycloadduct showed, besides the aromatic multiplet in the region (7.07-7.46, a triplet at δ 1.0 (J = 7.2 Hz) due to the methyl protons, a quartet at δ 4.07 (J = 7.2 Hz) corresponding to the methylene protons of CO_2Et, in addition to two doublets at δ 4.52 and at 5.03 ppm corresponding to the protons at C-4' and at C-4, respectively as well as a doublet of doublet at δ 4.93 corresponding to the proton at C-5'. These chemical shifts supported the 4,5'-bipyrazole **4**, where the chemical shift of the proton at the 5'-position in cycloadduct **4** appeared at a higher chemical shift than that at the 4'-position as shown in Figure 1. These chemical shifts of the protons at 4'- and 5'-positions in 4,5'-bipyrazole **4** are very similar to those reported for the C-4 and C-5 protons of analogous simple 4,5-dihydro-1*H*-pyrazole derivatives.[25-28] Also, the higher chemical shift of the proton at C-4 proton is due to the presence of two electron-withdrawing substituents at C-5. The low coupling constant values for the pyrazoline protons indicates that the protons exist exclusively in the *Z*-configuration.



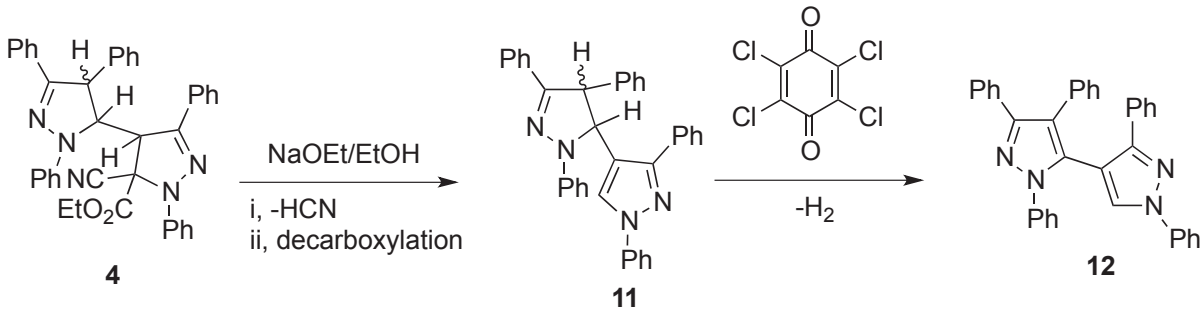
Scheme 1. Synthesis of the 4,5'-bipyrazole derivative **4**

Next, when the cycloadduct **4** was subjected to heating at an elevated temperature in boiling DMF, it underwent thermal elimination of hydrogen cyanide to afford the corresponding product; ethyl 1,3-diphenyl-4-(1,3,4-triphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxylate (**10**) in almost quantitative yield (Scheme 2).



Scheme 2. Synthesis of bipyrazole **10**

Heating bipyrazole **4** in ethanolic sodium ethoxide solution led to the formation of the partially aromatized 1,3-diphenyl-4-(1,3,4-triphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-1*H*-pyrazole (**11**) via elimination of hydrogen cyanide and subsequent decarboxylation (Scheme 3). Compound **11** was transformed into the fully aromatized 1',1,3,3',4'-pentaphenyl-1*H*,1'*H*-4,5'-bipyrazole (**12**) upon dehydrogenation when heated in the presence of tetrachloro-1,4-benzoquinone (chloranil).



Scheme 3. Synthesis of the bipyrazoles **11** and **12**

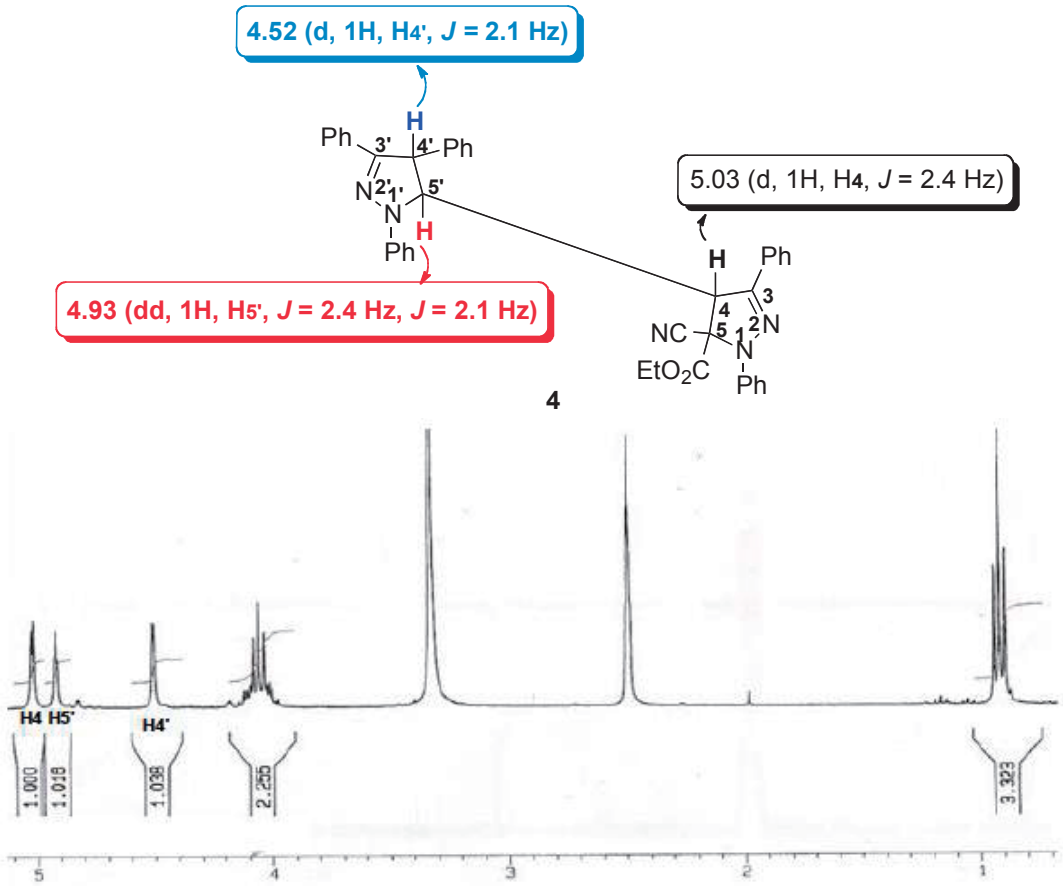


Figure 1. Proton chemical shifts and coupling constants of the regioisomer **4**

The DFT/B3PW91 level of calculation employing the 6-31G(d) basis set was used to carry out the quantum calculations. A full geometry optimization of the optimized structures of the different compounds under investigation was carried out as well as the geometry obtained were checked to be a minimum the following the hessian matrix eigen value. All the calculations were carried out using the Gaussian 03 program package.[29] One of the important criteria that are used to study the regioselectivity and reactivity in 1,3-dipolar cycloaddition, is to study the contribution of the sites of interaction between

reacting materials in their frontier molecular orbitals.[30,31] Therefore, analysis of the HOMO and LUMO of both reactants need to be considered. The optimized structures of the dipole **2** and the dipolarophile **3** along with their HOMO and LUMO values are depicted in Figure 2.

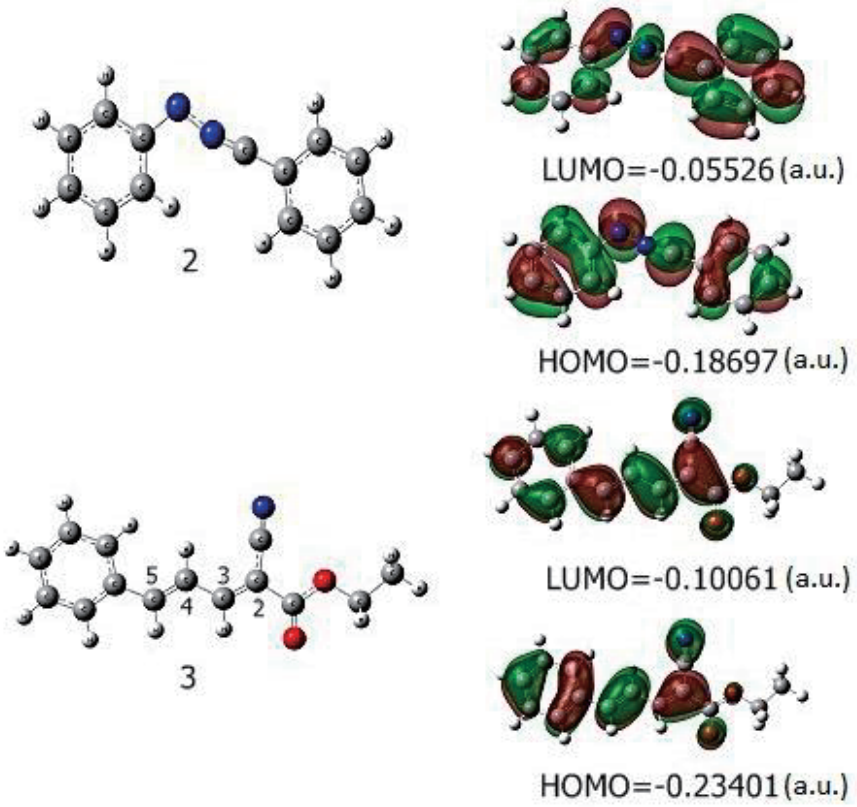


Figure 2. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compound **2** and compound **3** using B3PW91/6-31G(d) level of calculation

By investigating the frontier molecular orbital energies (a.u.) values as shown in Figure 2, one can observe that, based on the ΔE values between the HOMO and LUMO for both reactants that the reaction is following the normal electron demand procedure.[32,33]

Table 1 shows the atomic orbital coefficient for the reactive sites for both the dipole **2** and the dipolarophile **3**. It is well established that the atom with the largest orbital coefficient has the highest priority or probability to start the reaction.[34,35] From this point, we can see that the dipole **2** poses the nitrogen atom with the highest orbital coefficient, will start the interaction. Nevertheless, the active sites in the dipolarophile **3** is showing that for the sp^2 atoms C-2 and C-3 having close values (Table 1) of the orbital coefficient bearing nearly the same probability to a start the interaction with dipole molecule taking into account the symmetry which is an important factor either. In contrast, atoms C-4 and C-5 show a large variance between their orbital coefficients (Table 1). This gives the priority of C-5 to start the reaction and to stabilize the interaction. Thus, based on the date obtained for the these active sites

concerning the size of the orbitals and their symmetry, no clear decision could be taken for the structure which is mostly probable, with structure **7** seems to be the least. In addition to that, the reaction seems to proceed in a less or more synchronized way.

Table 1. Molecular orbital coefficients of the active centers involved in the reaction obtained using B3PW91/6-31G(d) level of calculation

Compound No.	**HOMO**				**LUMO**			
	Atom				**Atom**			
	C	**N**			**C**	**N**		
2	-0.27350	0.35894			0.15459	0.18846		
	C2	**C3**	**C4**	**C5**	**C2**	**C3**	**C4**	**C5**
3	0.27563	0.10141	-0.25081	-0.20898	0.26081	-0.28670	-0.15730	0.29912

The reactivity of different regions has been analyzed by means of Fukui indices since they indicate the form of the nucleophilic and electrophilic behavior of each atom in the molecule. Fukui function *f(r)* is the best way to change the number of electrons in a molecule.[36,37] The Fukui function is defined by Parr and Yang[38,39] as

$$f(r) = \left(\frac{\delta\rho(r)}{\delta N}\right)_v = \left(\frac{\delta\mu}{\delta v}\right)_N$$

where μ is electronic, chemical potential defined above, v is the external potential, ρ corresponds to the electronic density, and N is the total number of electrons of the system. The second formula for *f(r)*, written as $[\delta\rho(r)/\delta N]v$ shows that it is a quantity involving the electron density of the atom or molecule in its frontier valence regions. As $\rho(r)$ is discontinuous function of N, two different types of *f(r)* can be defined[40]:

$f+(r) = \rho N+1(r) - \rho N(r)$ for (nucleophilic attack)

$f-(r) = \rho N(r) - \rho N-1(r)$ for (electrophilic attack)

where $\rho N+1$, ρN, and $\rho N-1$ are the electronic densities of anionic, neutral and cationic species, respectively.

Thus, the Fukui indices for the sites for the dipolarophile **3** in the 1,3 cycloaddition in this study were calculated to show the regioselectivity of these sites. The results are depicted in Table 2.

Table 2. Local reactivity descriptors in atomic units for the dipolarophile (**3**)

Atomic symbols and numbering	*f*+	*f*-
C2	0.173	0.109
C3	-0.023	0.094
C4	0.107	0.023
C5	0.067	0.129

Figure 3 shows a mapped illustration for the ability of active centers of the cycloaddition reaction of compound **3** as obtained from the Fukui indices calculations.

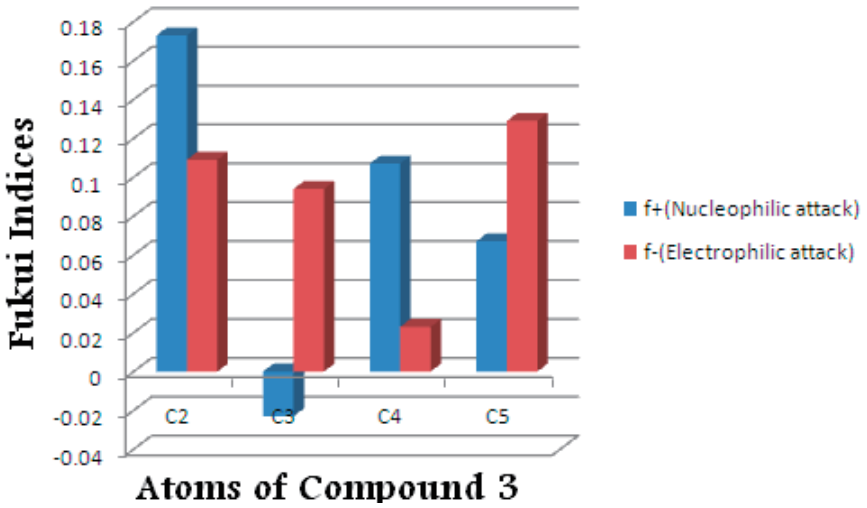


Figure 3. Comparison of the Fukui indices for the different sites for the cycloaddition in compound **3** as obtained from B3PW91/6-31G(d)

As inferred from Table 2 and Figure 3, Fukui indices for compound **3** which is the dipolarophile showing that C-2 is a preferred site for nucleophilic attack. Thus, it will be attacked by the negative charge on the nitrogen atom in the dipole **2**. In addition to that, C-3 is a preferred site for an electrophilic attack. Thus, it will be attacked with the positive charge on the dipole **2**. Based on this information we can exclude compounds **6** and **7** from the products to be obtained. By taking a look on C-4 and C-5 (Table 2), we can conclude from their Fukui indices that C-4 shows an ability for nucleophilic attack whereas C-5 is showing more tendency for the electrophilic attack and this give a preference for the structure **4** over structure **5** (Figure 4).

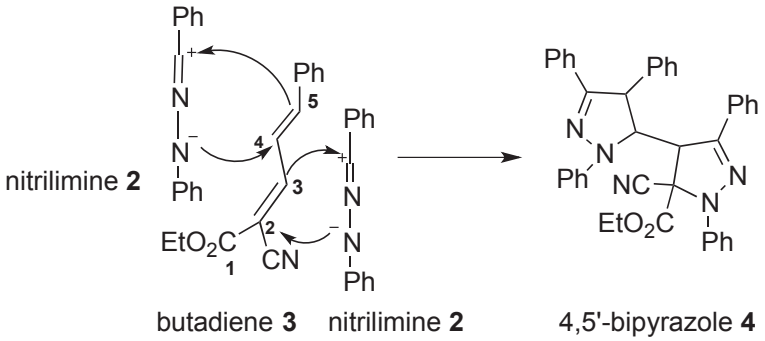


Figure 4. Regioselective addition of nitrilimine **2** to butadiene derivative **3**

Table 3 lists the heat of reaction *(ΔH* (298 k)) for the six possible products (**4**-**9**) calculated at the optimized geometries for both the possible products (**4**-**9**) and the isolated reactants (**2**) and (**3**), considering different possible ratios of interaction between the reactants as shown in Table 3. The values of *(ΔH* (298 k)) were obtained from the theoretical calculations employing the PM6 semi-empirical level of theory using MOPAC software[41] for the cycloaddition reaction routes as indicated in Scheme 1.

Table 3. The heat of formation *ΔHf* (298 k), for compound (**2**-**9**) and heat of reaction *ΔH* (298 k) for the different routes for the 1,3-cycloaddition reactions between compound (**3**) and compound (**2**) in (1:2) and (1:1) ratios as obtained from the PM6 semi-empirical level of theory

Compound	*ΔHf* (298 k) kcal/mol		Rx route	*ΔH* (298 k) reaction (*ΔHp*-*ΔHr*) kcal/mol
2	114.1708			
3	-5.263554			
4	165.56002		(3)+2(2) ⟶ (4)	-57.51802
5	166.63449	(1:2)	(3)+2(2) ⟶ (5)	-56.443543
6	171.24506		(3)+2(2) ⟶ (6)	-51.832976
7	166.88585		(3)+2(2) ⟶ (7)	-56.192189
8	101.20617	(1:1)	(3)+(2) ⟶ (8)	-7.701074
9	104.51748		(3)+(2) ⟶ (9)	-4.389757

As inferred from Table 3, all the values for the *ΔH* (298 k) *reaction* are predicted to be negative values indicating an exothermic behavior for the cycloaddition reactions between compound **3** and compound **2**. Furthermore, compound number **4** was found to be the most stable compound as inferred from its heat of reaction. Compound numbers **8** and **9** resulted from (1:1) route were found to be of less stability than those of the (1:2) route (Table 3). Based on the results obtained from the theoretical calculation discussed

above one can conclude that structure **4** is the one likely to exist, which is in agreement with the experimental results obtained.

CONCLUSION

We have successfully synthesized some new bipyrazole derivatives of biological and pharmacological interest, *via* 1,3-dipolar cycloaddition reactions. The regioselectivity in the 1,3-dipolar cycloaddition has been explained confirmed by computational studies.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded on potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT-IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H Spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyzes (C, H, N, S) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Ethyl (2*Z*,4*E*)-2-cyano-5-phenyl-2,4-pentadienoate (**3**),[21] and *N*'-phenylbenzohydrazonoyl chloride (**1**)[22] were prepared following procedures reported in the literature**.**

Synthetic Procedures

Synthesis of 5-ethoxycarbonyl-5-cyano-1',1,3,3',4'-pentaphenyl-4,4',5,5'-tetrahydro-1*H*,1'*H*-4,5'-bipyrazole (4).

Method A: An equimolar quantity of the ethyl (2*Z*,4*E*)-2-cyano-5-phenyl-2,4-pentadienoate (**3**) and hydrazonoyl chloride **1** (10 mmol each) were dissolved in dry benzene (15 mL). To the resulting solution, triethylamine (0.1 mL, 10 mmol) was added and the reaction mixture was stirred for 12 h at rt and then the solvent was distilled off under reduced pressure. The oil residue was triturated with MeOH and the formed solid product was collected by filtration, washed with MeOH and finally recrystallized from EtOH to afford the 4,5'-bipyrazole derivative **4** in 42% yield.

Method B: The above reaction was repeated using hydrazonoyl chloride **1** and the diene ester **3** in 2:1 molar ratios, in the presence of two equivalents of triethylamine under the same reaction condition. Triturating the product as above afforded a product identical in all respects (TLC, mp, mixed mp, and IR spectrum), with that obtained from the above procedure but with higher yield (68%).

Method C: The above reactions were repeated using hydrazonoyl chloride **1** and the diene ester **3**, in the presence of triethylamine under reflux condition. Triturating the product as above afforded a product identical in all respects (TLC, mp, mixed mp, and IR spectrum), with that obtained from the above two

procedures.

Mp 213-215 ºC; IR (KBr) ν 1600 (C=N), 1740 (C=O), 2940 (CH aliphatic), 3080 (CH aromatic) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.0 (t, 3H, CH_3, J = 7.1 Hz), 4.07 (q, 2H, CH_2, J = 7.1 Hz), 4.52 (d, 1H, J = 2.1 Hz), 4.93 (dd, 1H, J = 2.4, 2.1 Hz), 5.03 (d, 1H, J = 2.4 Hz), 7.07-7.46 (m, 25H, Ar-H); ^{13}C NMR (DEPT) (DMSO-d_6) δ 13.4 (CH_3), 63.3 (CH_2), 53.2, 54.1, 68.8, 70.6, 112.8, 114.7, 117.8, 119.4, 123.6, 125.7, 126.6, 127.2, 127.5, 127.7, 128.3, 128.6, 129, 129.3, 129.5, 129.9 (CH-Ar), 130.3, 130.7, 139.2, 142.3, 143.1, 150.3, 151.7, 162.7; MS *m/z* (%) 615 (M^+, 0.1), 589 (2.2). Anal. Calcd for $C_{40}H_{33}N_5O_2$: C, 78.03; H, 5.40; N, 11.37. Found: C, 78.12; H, 5.47; N, 11.29%.

Synthesis of ethyl 1,3-diphenyl-4-(1,3,4-triphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxylate (10).

To a solution of bipyrazole **4** (0.62 g, 1 mmol) in DMF (10 mL), was added piperidine (0.1 mL) and the mixture was heated at reflux for 1 h, and then left to cool to room temperature. The reaction mixture was then diluted with water and the precipitated solid was collected by filtration, washed with water, dried and finally crystallized from dioxane to afford **10** (94% yield), mp 153-154 ºC; IR (KBr) ν 1596 (C=N), 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.2 Hz), 3.97 (q, 2H, J = 7.2 Hz), 5.03 (d, 1H, J = 3.6 Hz), 5.37 (d, 1H, J = 3.6 Hz), 6.75-7.72 (m, 25H, ArH). Anal. Calcd for $C_{39}H_{32}N_4O_2$: C, 79.57; H, 5.48; N, 9.52. Found: C, 79.51; H, 5.53; N, 9.59%.

Synthesis of 1,3-diphenyl-4-(1,3,4-triphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-1*H*-pyrazole (11).

A solution of the bipyrazole **4** (2.46 g, 4 mmol) in sodium ethoxide [prepared from sodium metal (0.14 g, 6 mmol) in EtOH (25 mL)] was heated under reflux for 1 h, then left to cool. The precipitated solid was collected by filtration, washed with water, dried and finally recrystallized from EtOH to afford **11** (77% yield), mp 202-203 ºC; IR (KBr) ν 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52 (d, 1H, J = 3.8 Hz), 5.42 (d, 1H, J = 3.8 Hz), 6.83-7.72 (m, 26H, ArH); MS *m/z* (%) 520 (1.3), 519 (9.2), 518 (39.0), 517 (100%), 516 (M^+, 9.8), 515 (1.5). Anal. Calcd for $C_{36}H_{28}N_4$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.61; H, 5.40; N, 10.89%.

Synthesis of 1',1,3,3',4'-pentaphenyl-1*H*,1'*H*-4,5'-bipyrazole (12).

A mixture of compound **11** (0.516 g, 1 mmol) and tetrachloro-1,4-benzoquinone (0.5 g, 2 mmol) was refluxed in xylene (10 mL) for 24 h. The solvent was removed under reduced pressure and the residue was stirred with an aqueous solution of sodium hydroxide (5%, 60 mL) for 30 min then filtered, washed with water and dried. Recrystallization from DMF afforded **9**, yield 73%, mp > 300 ºC, IR (KBr) ν 1602 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.11-7.51 (m, ArH). Anal. Calcd for $C_{36}H_{26}N_4$: C, 84.02; H, 5.09; N, 10.89. Found: C, 84.08; H, 5.15; N, 10.82%.

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