Highly Regioselective Synthesis of Novel 1,4'-Bipyrazoles

Marcos A. P. Martins,* Gabriela F. Fiss, Clarissa P. Frizzo, Fernanda A. Rosa, Helio G. Bonacorso and Nilo Zanatta

*Núcleo de Química de Heterociclos, Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria-RS, Brazil

Este trabalho descreve a síntese de 1,4'-bipirazóis inéditos pela da reação de ciclocondensação de novas β-dimetilaminoenonas com as monoidrato de hidrazina, tert-butil hidrazina, fenil hidrazina, carbboximetilhidrazina. Os produtos foram obtidos com alta regiosseletividade em rendimentos de bons a moderados (50-80%). A técnica de cristalografia de raios-X foi utilizada para a elucidação da regiosseletividade da formação dos produtos. 1,4'-Bipirazolilisoxazóis também foram descritos.

Novel 1,4'-bipyrazoles were synthesized via highly regioselective cyclocondensation reactions of β-dimethylaminoenones with hydrazine monohydrate, tert-butylhydrazine hydrochloride, phenylhydrazine hydrochloride or carboxymethylhydrazine. X-ray diffraction technique was used in the elucidation of the regiochemistry of the β-dimethylaminoenamines and of the 1,4'-bipyrazoles. 1,4'-Bipyrazolylisoxazoles were also reported.

Keywords: enamiones, bipyrazoles, heterocycles, cyclocondensation, regioselectivity

Introduction

Many heterocyclic compounds have interesting biological activities. Pyrazoles and isoxazoles figure prominently in this regard. The recent success of a pyrazole COX-II inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry. The past few years have also witnessed explosive developments in combinatorial chemistry and solid-phase synthesis. Currently, there is a particular interest in bipyrazoles substituted in studies on intermolecular interactions with the participation of pyrazoles and their derivatives. The structure of pyrazole molecules, containing the fragment RN–N(H)–, is favorable in the formation of various hydrogen bonded complexes and associates in solid-cyclic dimers, trimers and tetramers, linear chains and helices, depending on the substituent. A literature survey turned up a few reports on 1,4'-bipyrazole and isoxazole synthesis and structure. The most promising method is a four-steps synthesis via the cyclization of an α-oxo-α-(3,5-dimethyl-1H-pyrazole-1-yl ketene dithioacetal with hydrazine monohydrate or phenylhydrazine in refluxing ethanol. 1,4'-Bipyrazoles have been also prepared by the reaction of 2-pyrazolyl-3-dimethylamino acrylate and acrylonitrile with hydrazine monohydrate and phenylhydrazine hydrochloride under microwave irradiation conditions. Our research group has been dedicated to the development of synthetic routes to heterocyclic compounds for around twenty years. We have extensively explored the potential of enones such as: 4-alkoxy-1,1,1-trihalo-3-alken-2-ones and enamiones as building blocks in cyclocondensation reactions. Our results have shown that the obtainment of heterocycles with high regioselectivity is generally dependent on the structure of the building block and sometimes it is dependent on the reaction conditions. Now we are interested in finding an alternative route to 1,4'-bipyrazoles and 1,4'-bipyrazolylisoxazoles. In view of the formation of new bonds C–C or C–N especially in the 4-position of the pyrazolyl ring, herein we reported our investigation in the regioselectivity of the cyclocondensation reactions of β-dimethylaminoenones with different 1,2-dinucleophiles such as hydrazine monohydrate, tert-butylhydrazine hydrochloride, phenylhydrazine hydrochloride, carboxymethylhydrazine and hydroxylamine hydrochloride by a three-steps procedure (alkylation, condensation and cyclocondensation reactions, respectively) to obtain the respective azoles in good yields. (Scheme 1).
Results and Discussion

The first step involves the synthesis of 2-(3,5-dimethyl-1H-1-pyrazolyl)acetophenone 2a (71% yield) and 3-(3,5-dimethyl-1H-1-pyrazolyl)acetophenone 2b (75% yield) through the alkylation reactions of 3,5-dimethyl-1H-pyrazole with 2-bromoacetophenone 1a and 2-bromopropiophenone 1b, respectively, under reflux of anhydrous acetone containing potassium carbonate for 5 h.¹⁷ The second step consists of the condensation reactions of these compounds with 1.2 equivalents of neat N,N-dimethylformamide dimethylacetal (DMFDMA) under reflux for 10 h. After removal of the excess reagent, 3-dimethylamino-2-(3,5-dimethyl-1H-1-pyrazolyl)-1-phenyl-2-propen-1-one 3a (92% yield) and 3-dimethylamino-2-(3,5-dimethyl-1H-1-pyrazolylmethyl)-1-phenyl-2-propen-1-one 3b (98% yield) were obtained.

Although carbanions resulting from proton abstraction from N-alkylpyrazoles might also be stabilized by the electron-attracting inductive effect of the ring nitrogen, the reactivity of such a species towards N,N-dimethylformamide dimethylacetal was demonstrated. The structure of the compounds was determined by ¹H NMR and ¹³C NMR spectroscopy, MS spectrometry, and HRMS analysis. Moreover, X-ray crystallography data confirmed the structure of compound 3b. By carrying out a single crystal X-ray analysis, E-configuration of the products was unequivocally determined, showing that a single isomer was obtained (Figure 1).

In the last step, the β-dimethylaminoenones were converted to 1,4'-bipyrazoles by treatment with hydrazine monohydrate, tert-butylhydrazine hydrochloride, phenylhydrazine hydrochloride and carboxymethylhydrazine. When the β-dimethylaminoenones 3a-b reacted with hydrazine monohydrate in ethanol at room temperature for 5 h, the corresponding 1,4'-bipyrazoles 4a (71% yield) and 4b (80% yield) were obtained; and when reacted with tert-butylhydrazine hydrochloride or phenylhydrazine hydrochloride in ethanol at 60 °C for 5 h, 1,4'-bipyrazoles 5a-b and 6a-b were obtained, respectively. After an initial screen of solvents and reaction temperatures, the 1,4'-bipyrazole 7a was synthesized by the cyclocondensation reaction of the β-dimethylaminoenone 3a with carboxymethylhydrazine and the use of one equivalent of BF₃•OEt₂ in anhydrous MeOH under reflux for 10 h in 72% yield. On the other hand, the reaction of the β-dimethylaminoenone 3b with carboxymethylhydrazine using these conditions did not give the expected 1,4'-bipyrazole 7b. Our preparative results are summarized in Scheme 1 and Table 1.

**Table 1.** Reaction conditions to synthesis of the 1,4'-bipyrazoles 4-7

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Z</th>
<th>n</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>NH₂NH₂H₂O,</td>
<td>NH</td>
<td>1</td>
<td>4a</td>
<td>71</td>
</tr>
<tr>
<td>EtOH, rt, 5 h</td>
<td>NH</td>
<td>2</td>
<td>4b</td>
<td>80</td>
</tr>
<tr>
<td>BuNHNH₂HCl</td>
<td>NBu</td>
<td>1</td>
<td>5a</td>
<td>50</td>
</tr>
<tr>
<td>EtOH, 60 °C, 5 h</td>
<td>NBu</td>
<td>2</td>
<td>5b</td>
<td>66</td>
</tr>
<tr>
<td>PhNHNH₂HCl</td>
<td>NPh</td>
<td>1</td>
<td>6a</td>
<td>64</td>
</tr>
<tr>
<td>EtOH, 60 °C, 5 h</td>
<td>NPh</td>
<td>2</td>
<td>6b</td>
<td>67</td>
</tr>
<tr>
<td>NH₂NH₂CO₂Me,</td>
<td>NCO₂Me</td>
<td>1</td>
<td>7a</td>
<td>72</td>
</tr>
<tr>
<td>BF₃•OEt₂, MeOH,</td>
<td>NCO₂Me</td>
<td>2</td>
<td>7b</td>
<td>&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield of isolated products; <sup>b</sup> Product was not identified.

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Figure 1. ORTEP of the compound 3b.
The highly regioselective cyclocondensation reactions of the β-dimethylaminoenones 3a-b with different hydrazines gave 1,5-regioisomer rather than the potential 1,3-regioisomer. Moreover, the regiochemistry of the compound 5b was unequivocally determined by single crystal X-ray diffraction data, confirming the formation of the 1,5-regioisomer as a single product (Figure 2).

Thus, the β-dimethylaminoenones 3a-b reacted with different hydrazines to afford, in each case, only one of the two possible regioisomers. Similarly, when the β-dimethylaminoenone 3a reacted with hydroxylamine hydrochloride in ethanol at 60 °C for 5 h, the 1,5-regioisomer of the 1,4'-bipyrazoylisoxazole (8a) was obtained with high regioselectivity in 61% yield. When the β-dimethylaminoenone 3b reacted with hydroxylamine hydrochloride in ethanol at 60 °C for 5 h, the 1,5-regioisomer of the 1,4'-bipyrazoylisoxazole (8b) was obtained in 50% yield. Therefore, we can say that the cyclocondensation reactions of the β-dimethylaminoenones 3a and 3b with hydroxylamine hydrochloride in these conditions are highly regioselective in both cases. Our preparative results are summarized in Scheme 2.

The same synthetic route was repeated via the synthesis of (3,5-dimethyl-1H-1-pyrazolyl)acetone 2c (Scheme 3).

Thus, the compound 2c was synthesized by the alkylation reaction of 3,5-dimethyl-1H-pyrazole with chloroacetone 1c in the presence of triethylamine under reflux of anhydrous toluene for 5 h in 67% yield. Then the compound 2c condensed with 1.2 equivalents of neat DMFDMA under reflux of toluene for 48 h. After removal of the excess reagent, the 4-dimethylamino-3-(3,5-dimethyl-1H-1-pyrazolyl)-3-buten-2-one 3c was obtained in 94% yield. Although the condensation reaction with two equivalents of DMFDMA may in theory lead to a mixture of 3c and 3c’ (Figure 3), in our experiment only 3c was formed. The 1H NMR spectra of 3c revealed the presence of a singlet corresponding to methyl at δ 2.25, and the absence of the two olefinic doublets, which would be observed in the 1H NMR spectra of 3c’. The β-dimethylaminoenone 3c was used as starting material for the synthesis of the 1,4'-bipyrazole 4c through the cyclocondensation reaction with hydrazine monohydrate in ethanol at room temperature for 5 h resulting in the product with 71% yield.

![Figure 2. ORTEP of the compound 5b.](image1)

![Scheme 2.](image2)

![Scheme 3.](image3)

![Figure 3. Theoretical product from dicondensantion.](image4)
Conclusions

The β-dimethylaminoenones 3a-c were synthesized via highly regioselective condensation reactions. A convenient synthetic route to 1,4'-biazoles, containing a variety of neutral, electron-donating and electron-withdrawing substituents, by a simple procedure from the β-dimethylaminoenones 3a-c is now available. Studies on the syntheses of other heterocyclic rings from 3a-c are in progress.

Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The indicated solvents were dried and purified according to recommended procedures. The 1H and 13C NMR spectra were acquired on a Bruker DPX 200 or Bruker DPX 400 spectrometer (1H at 200.13 MHz or 400.13 MHz and 13C at 50.32 MHz or 100.61 MHz, respectively), in 5 mm tube, and CDCl3 was used as solvent, containing TMS as internal standard at 298 K (digital resolution of ± 0.01 ppm). The mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked to a HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium as carrier gas. The high-resolution mass spectrum was obtained from a MicroTOF Ic Bruker Daltonics (Instituto de Química, Universidade de São Paulo, Brazil). The melting points were measure using a Microquímica MQAPF 301. The melting points were not corrected.

General procedure for synthesis of 2a-b

A mixture of 2-bromoacetophenone 1a or 3-bromopropiophenone 1b (20 mmol), 3,5-dimethyl-1H-pirazole (20 mmol) and potassium carbonate (20 mmol) was stirred at reflux temperature of anhydrous acetonitrile (20 mL) for 5 h. Then the mixture was filtered, extracted with dichloromethane (20 mL) and washed with water (3 × 20 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The products 2a-b were purified by recrystallization in hexane as solvent.

2-(3,5-Dimethyl-1H-1-pyrazolyl)acetophenone (2a)

mp 76-79 °C (from hexane) (lit.17 90-91 °C); 1H NMR (400 MHz, CDCl3/TMS, 25 °C) δ 2.15 (s, 3 H, Me), 2.23 (s, 3 H, Me), 5.45 (s, 2 H, CH2), 5.90 (s, 1 H, CH), 7.49 (t, JH,H = 7.7 Hz, 2 H, Ph), 7.61 (t, JH,H = 7.1 Hz, 1 H, Ph), 7.97 (d, JH,H = 7.4 Hz, 2 H, Ph) ppm; 13C NMR (100 MHz, CDCl3/TMS, 25 °C) δ 10.9 (Me), 13.4 (Me), 55.2 (CH2), 105.8, 140.4, 148.2 (1H-1-pyrazolyl), 128.0, 128.8, 129.6, 131.3 (Ph), 192.7 (CO) ppm; MS (EI, 70 eV) m/z 214 (M+, 5%), 199 (2), 185 (100); HRMS (ESI+) m/z [M + H]+ calc. for C15H14N2O: 215.1184; found: 215.1185.

3-(3,5-Dimethyl-1H-1-pyrazolyl)propiofenona (2b)

mp 59-62 °C (from hexane); 1H NMR (400 MHz, CDCl3/TMS, 25 °C) δ 2.19 (3 H, Me), 2.29 (3 H, Me), 3.56 (t, JH,H = 6.8 Hz, 2 H, CH2), 3.97 (t, JH,H = 6.8 Hz, 2 H, CH2), 5.74 (s, 1 H, CH), 8.44 (t, JH,H = 8.4 Hz, 2 H, Ph), 7.55 (t, JH,H = 7.4 Hz, 1 H, Ph), 7.93 (d, JH,H = 7.1 Hz, 2 H, Ph) ppm; 13C NMR (50 MHz, CDCl3/TMS, 25 °C) δ 10.9 (Me), 13.3 (Me), 38.6 (CH2), 42.8 (CH2), 104.6, 139.1, 147.5 (1H-1-pyrazolyl), 127.9, 128.4, 133.2, 136.2 (Ph), 197.6 (CO) ppm; MS (EI, 70 eV) m/z 228 (M+, 14%), 123 (100); HRMS (ESI+) m/z [M + H]+ calc. for C14H16N2O: 229.1341; found: 229.1343.

Procedure for synthesis of 2c

A mixture of chloroacetone 1c (10 mmol), 3,5-dimethyl-1H-pirazole (10 mmol) and triethylamine (10 mmol) was stirred at reflux temperature of anhydrous toluene (3 mL) for 5 h. Then the mixture was extracted with dichloromethane (10 mL) and washed with water (3 × 10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The product 2c was purified by recrystallization in hexane as solvent.

(3,5-Dimethyl-1H-1-pyrazolyl)acetone 2c

mp 49-51 °C (from hexane) (lit.26 67-68 °C); 1H NMR (200 MHz, CDCl3/TMS, 25 °C) δ 2.10 (s, 3 H, Me), 2.16 (s, 3 H, Me), 2.22 (s, 3 H, Me), 4.76 (s, 2 H, CH2), 5.89 (s, 1 H, CH) ppm; 13C NMR (50 MHz, CDCl3/TMS, 25 °C) δ 10.9 (Me), 13.4 (Me), 26.8 (Me), 58.3 (CH2), 105.9, 139.8, 148.4 (1H-1-pyrazolyl), 203.0 (CO) ppm; MS (EI, 70 eV) m/z 152 (M+, 49%), 137 (1), 109 (100); HRMS (ESI+) m/z [M + H]+ calc. for C8H10N2O: 153.1028; found: 153.1023.

General procedure for synthesis of β-dimethylaminoenones 3a-b

2-(3,5-Dimethyl-1H-1-pyrazolyl)acetophenone 3a or 3-(3,5-dimethyl-1H-1-pyrazolyl)propiofenona 3b (10 mmol) was stirred at reflux temperature of DMFDMMA (12 mmol) for 10 h. Then the mixture was submitted at reduced pressure for 1 h. The product 3a was purified by filtration in a column chromatographic silica gel with dichloromethane as an eluent, and the product 3b was purified by recrystallization in ethyl acetate as solvent.
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#### General Procedure for synthesis of 1,4'-bipyrazoles 4a-c

A mixture of β-dimethylaminoenone 3a, 3b or 3c (1 mmol), hydrazine monohydrate (1.2 mmol) and ethanol (1 mmol) was stirred at room temperature for 5 h. Then the mixture was extracted with dichloromethane (3 mL) and washed with water (3 × 3 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The products 4a-c were purified by filtration in a column chromatographic silica gel with dichloromethane as an eluent.

#### 3,5-Dimethyl-5'-phenyl-1H,1'-4'-bipyrazole (4a)

Oil; 1H NMR (200 MHz, CDCl₃/TMS, 25 °C) δ 1.88 (s, 3 H, Me), 2.31 (s, 3 H, Me), 5.95 (s, 1 H, CH), 7.25-7.35 (m, 6 H, Ph and NH), 7.67 (s, 1 H, CH) ppm; 13C NMR (100 MHz, CDCl₃/TMS, 25 °C) δ 11.1 (Me), 13.4 (Me), 105.8, 125.7, 128.2, 128.6, 128.9, 129.7, 132.3, 141.9, 143.2, 149.2 (2 × 1H-1-pyrazolyl and Ph) ppm; MS (EI, 70 eV) m/z 238 (M⁺, 49%), 223 (100); HRMS (ESI+) m/z [M + H]⁺ calc. for C₁₉H₁₈N₃O: 293.1296; found: 293.1292.

#### 1-(3,5-Dimethyl-1H-1-pyrazolyl)-1-(5-phenyl-1H-4-pyrazolyl)methane (4b)

Oil; 1H NMR (200 MHz, CDCl₃/TMS, 25 °C) δ 1.97 (s, 3 H, Me), 2.19 (s, 3 H, Me), 5.14 (s, 2 H, CH₂), 5.76 (s, 1 H, CH), 7.14 (br s, 1 H, NH), 7.26-7.34 (m, 4 H, Ph and CH), 7.41-7.46 (m, 2 H, Ph) ppm; 13C NMR (100 MHz, CDCl₃/TMS, 25 °C) δ 10.7 (Me), 13.3 (Me), 43.5 (CH₃), 105.2, 114.6, 127.8, 127.9, 128.1, 128.5, 131.4, 133.7, 138.8, 147.4 (2 × 1H-1-pyrazolyl and Ph) ppm; MS (EI, 70 eV) m/z 252 (M⁺, 41%), 223 (1), 157 (100); HRMS (ESI+) m/z [M + H]⁺ calc. for C₁₉H₁₈N₃O: 253.1453; found: 253.1455.

#### 3,5-Dimethyl-5'-methyl-1H,1'-4'-bipyrazole (4c)

Oil; 1H NMR (400 MHz, CDCl₃/TMS, 25 °C) δ 2.12 (s, 3 H, Me), 2.15 (s, 3 H, Me), 2.28 (s, 3 H, Me), 5.95 (s, 1 H, CH), 7.55 (s, 1 H, CH) ppm; 13C NMR (100 MHz, CDCl₃/TMS, 25 °C) δ 9.6 (Me), 11.3 (Me), 13.4 (Me), 105.3, 105.3, 141.4, 141.4, 148.9, 148.9 (2 × 1H-1-pyrazolyl) ppm; MS (EI, 70 eV) m/z 176 (M⁺, 100%), 161 (6), 148 (8), 134 (24), 81 (15), 66 (12); HRMS (ESI+) m/z [M + H]⁺ calc. for C₁₉H₁₈N₃O: 277.1140; found: 277.1137.

#### General procedure for synthesis of 1,4'-biazoles 5a-b, 6a-b and 8a-b

A mixture of β-dimethylaminoenone 3a or 3b (1 mmol), tert-butylhydrizine hydrochloride, phenylhydrizine hydrochloride or hydroxylamine hydrochloride (1.2 mmol) and ethanol was stirred at 60 °C for 5 h. Then the mixture
was extracted with dichloromethane (3 mL) and washed with water (3 × 3 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The oil products were purified by filtration in a column chromatographic silica gel with dichloromethane as an eluent, and the product 5b was purified by recrystallization in hexane as solvent.

1′-(tert-Butyl)-3,5-dimethyl-5′-phenyl-1′H-1,4′-bipyrazole (5a)

Oil; 'H NMR (400 MHz, CDCl3/TMS, 25 °C) δ 1.48 (s, 9 H, tBu), 2.14 (s, 3 H, Me), 2.24 (s, 3 H, Me), 5.52 (s, 1 H, CH), 7.31 (m, 5 H, Ph), 7.62 (s, 1 H, CH) ppm; 13C NMR (100 MHz, CDCl3/TMS, 25 °C) δ 10.9 (Me), 13.3 (Me), 30.9, 68.7 (tBu), 105.9, 127.8, 128.1, 128.3, 128.9, 129.9, 130.7, 133.1, 133.9, 148.3 (2 × 1H-1-pyrazolyl and Ph) ppm; MS (EI, 70 eV) m/z 294 (M+, 100%), 279 (2), 237 (29), 223 (83), 209 (6), 143 (6); HRMS (ESI+) m/z [M + H]+ calc. for C18H22N4: 295.1922; found: 295.1920.

1-(1-(tert-Butyl)-5-phenyl-1H-4-pyrazolyl)-1-(3,5-dimethyl-1H-1-pyrazolyl)methane (5b)

mp 101-104 °C (from hexane); 'H NMR (400 MHz, CDCl3/TMS, 25 °C) δ 1.41 (s, 9 H, tBu), 1.85 (s, 3 H, Me), 2.17 (s, 3 H, Me), 4.70 (s, 2 H, CH2), 5.67 (s, 1 H, CH), 7.23-7.25 (m, 2 H, Ph), 7.38 (s, 1 H, CH), 7.39-7.42 (m, 3 H, Ph) ppm; 13C NMR (100 MHz, CDCl3/TMS, 25 °C) δ 10.7 (Me), 13.4 (Me), 30.9, 61.2 (tBu), 43.0 (CH3), 104.8, 117.9, 128.1, 128.4, 128.7, 130.9, 130.7, 133.2, 136.3, 138.5, 147.1 (2 × 1H-1-pyrazolyl and Ph) ppm; MS (EI, 70 eV) m/z 308 (M+, 14%), 293 (1), 213 (19), 157 (100); HRMS (ESI+) m/z [M + H]+ calc. for C18H22N4: 309.2079; found: 309.2078.

1′,5′-Diphenyl-3,5-dimethyl-1′H-1,4′-bipyrazole (6a)

Oil; 'H NMR (400 MHz, CDCl3/TMS, 25 °C) δ 1.79 (s, 3 H, Me), 2.28 (s, 3 H, Me), 5.84 (s, 1 H, CH), 6.99-7.02 (m, 2 H, Ph), 7.19-7.24 (m, 3 H, Ph), 7.3-7.33 (m, 5 H, Ph), 7.88 (s, 1 H, CH) ppm; 13C NMR (100 MHz, CDCl3/TMS, 25 °C) δ 11.1 (Me), 13.6 (Me), 105.5, 122.1, 127.7, 127.8, 128.5, 128.7, 128.9, 129.0, 125.2, 138.2, 138.7, 141.5, 149.1, 139.8 (2 × 1H-1-pyrazolyl and 2 × Ph) ppm; MS (EI, 70 eV) m/z 314 (M+, 100%), 285 (1); HRMS (ESI+) m/z [M + H]+ calc. for C32H24N4: 315.1609; found: 315.1609.

1-(3,5-Dimethyl-1H-1-pyrazolyl)-1-(1,5-diphenyl-1H-4-pyrazolyl)methane (6b)

Oil; 'H NMR (200 MHz, CDCl3/TMS, 25 °C) δ 1.95 (s, 3 H, Me), 2.23 (s, 3 H, Me), 5.06 (s, 2 H, CH2), 5.76 (s, 1 H, CH), 7.16-7.26 (m, 7 H, Ph), 7.35-7.38 (m, 3 H, Ph), 7.59 (s, 1 H, CH) ppm; 13C NMR (50 MHz, CDCl3/TMS, 25 °C) δ 10.7 (Me), 13.1 (Me), 43.1 (CH3), 105.5, 117.1, 119.7, 124.6, 127.1, 128.6, 128.7, 128.7, 128.8, 129.4, 129.6, 129.9, 140.1 (2 × 1H-1-pyrazolyl and 2 × Ph) ppm; MS (EI, 70 eV) m/z 328 (M+, 14%), 233 (100), 219 (3); HRMS (ESI+) m/z [M + H]+ calc. for C32H24N4: 329.1766; found: 329.1769.

4-(3,5-Dimethyl-1H-1-pyrazolyl)-5-phenylisoxazole (8a)

Oil; 'H NMR (200 MHz, CDCl3/TMS, 25 °C) δ 1.92 (s, 3 H, Me), 2.31 (s, 3 H, Me), 5.99 (s, 1 H, CH), 7.32-7.35 (m, 3 H, Ph), 7.40 (m, 2 H, Ph), 8.74 (s, 1 H, CH) ppm; 13C NMR (50 MHz, CDCl3/TMS, 25 °C) δ 11.1 (Me), 13.5 (Me), 106.8, 126.1, 126.8, 127.2, 128.9, 129.1, 130.3, 150.5, 156.4, 158.2 (2 × 1H-1-pyrazolyl and Ph) ppm; MS (EI, 70 eV) m/z 239 (M+, 100%), 210 (46), 144 (44); HRMS (ESI+) m/z [M + H]+ calc. for C14H13NO: 240.1137; found: 240.1137.

1-(3,5-Dimethyl-1H-1-pyrazolyl)-1-(5-phenyl-4-isoxazolyl)methane (8b)

Oil; 'H NMR (400 MHz, CDCl3/TMS, 25 °C) δ 2.05 (s, 3 H, Me), 2.21 (s, 3 H, Me), 5.19 (s, 1 H, CH), 5.82 (s, 2 H, CH2), 7.49-7.52 (m, 3 H, Ph), 7.67-7.69 (m, 2 H, Ph), 7.96 (s, 1 H, CH) ppm; 13C NMR (50 MHz, CDCl3/TMS, 25 °C) δ 10.8 (Me), 13.3 (Me), 42.2 (CH3), 105.9, 111.6, 125.7, 127.1, 129.0, 130.2, 138.9, 148.1, 151.1, 164.5 (1H-1-pyrazolyl, Ph and isoxazolyl) ppm; MS (EI, 70 eV) m/z 253 (M+, 100%), 238 (8), 224 (17), 158 (37); HRMS (ESI+) m/z [M + H]+ calc. for C18H15N3O: 254.1293; found: 254.1296.

Experimental procedure for synthesis of 1′,4′-bipyrazole 7a

A mixture of β-dimethylaminooenone 3a (1 mmol), carboxymethylhydrzone (1.2 mmol) and BF3·OEt2 (1.2 mmol) was stirred at reflux temperature of methanol (1 mL) for 10 h. Then the mixture was extracted with dichloromethane (3 mL) and washed with water (3 × 3 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The product 7a was purified by filtration in a column chromatographic silica gel with dichloromethane as an eluent.

3,5-Dimethyl-5′-phenyl-1′-methylcarboxyl-1′H-1,4′-bipyrazole (7a)

Oil; 'H NMR (400 MHz, CDCl3/TMS, 25 °C) δ 2.07 (s, 3 H, Me), 2.21 (s, 3 H, Me), 3.85 (s, 1 H, OMe), 5.14 (s, 1 H, CH), 7.33 (s, 1 H, CH), 7.37-7.39 (m, 5 H, Ph) ppm;
For example, there are 2292 pyrazoles and 906 isoxazoles in
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References

1. For example, there are 2292 pyrazoles and 906 isoxazoles in
the MDL Drug Report (MDDR-3D, 99.2), representing 3.0% of
entries. They are 1.6% of entries in Comprehensive Medicinal
Chemistry (CMC-3D 99.1). Both databases are from MDL
Information Systems.

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18. Crystallographic data for the structural analysis of the compounds 3b and 5b, reported in this paper, have been
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(CCDC) under the numbers 680984 and 680985, respectively.
Copies of the information may be obtained, free of charge, from