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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7557–7561

Synthesis of new diheteroarylcarbazoles: a facile and simple route of 3,6-di(pyrazol-4-yl)carbazoles

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Received 4 July 2006; revised 12 August 2006; accepted 23 August 2006

Abstract—A short and facile route to the synthesis of new 3,6-di(pyrazol-4-yl)carbazoles is reported. Dipyrazolylcarbazoles were synthesized in two steps from 3,6-diacetylcarbazoles through a Vilsmeier reaction which led to the formation of carbazolyl-β-chlorovinyl aldehydes, followed by cyclization with hydrazine hydrate. The reaction of the Vilsmeier reagent with hydrazones of diacetylcarbazoles yielded the corresponding pyrazole dicarbaldehydes in good yields.

Natural products comprising a carbazole skeleton fused with another heterocycle have received significant attention due to the promising antitumor properties of several of their representatives. Numerous total syntheses of these natural compounds have been accomplished as well as structural modifications for annulating various heterocyclic systems to carbazole.[1] The rapidly growing class of heteroaryl-condensed carbazoles has begun to attract increasing interest because of their broad spectrum of useful biological activities.[2]

Most heteroarylcarbazoles reported in the literature contain a heteroaryl moiety fused with a carbazole; however, there are few reports where the heteroaryl moiety is substituted with a carbazole unit. Hence, a practical method for the preparation of such compounds is desirable (see Figs. 1–3).

Pyrazole derivatives have been reported as pharmaceuticals for the treatment of cerebrovascular disorders[3] and for their antiarrhythmic, sedative, and platelet anti-aggregating activities.[4] This promising biological activity prompted us to introduce pyrazoles in the 3,6-positions of 9-alkylcarbazoles. Biologically active 3-substituted and 3,6-disubstituted carbazoles have been reported in the literature.[5]

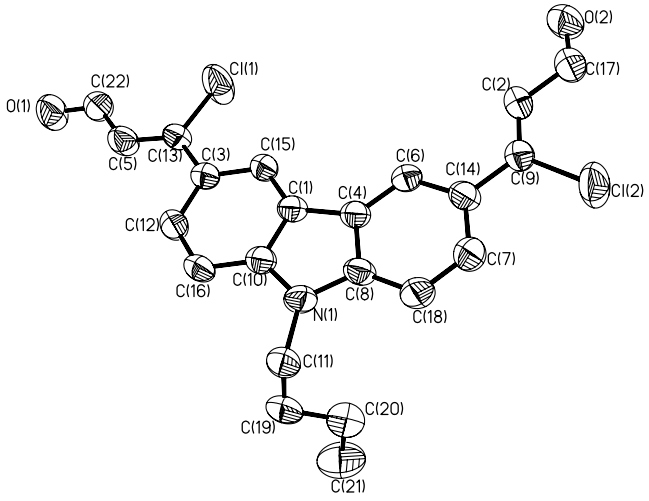

Figure 1. ORTEP diagram of 3-chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-butyl-9*H*-carbazol-3-yl]propenal **2c**.

A survey of the literature revealed that the main methods for the construction of pyrazole rings consist of the reaction between hydrazines and β-difunctional compounds[6] or 1,3-dipolar cycloadditions of diazo compounds onto triple bonds.[7] We herein report a short synthesis of 3,6-di(pyrazol-4-yl)carbazoles from 3,6-diacetylcarbazoles.

The carbazolyl-β-chlorovinylaldehydes[8] were readily prepared from 9-alkyl-3,6-diacetylcarbazoles[9] using the Vilsmeier reagent, for example, reaction of 9-methyl-3,6-diacetylcarbazole **1a** with DMF/$POCl_3$ gave

Keywords: Diheteroarylcarbazoles; Dipyrazolylcarbazoles; Vilsmeier reagent; β-Chlorovinylaldehydes; Hydrazone cyclization.
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doi:10.1016/j.tetlet.2006.08.087

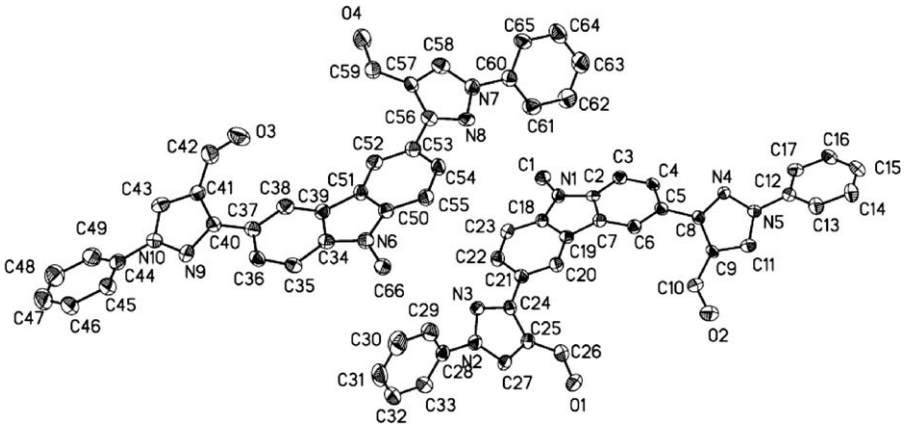


Figure 2. ORTEP diagram of 3-[6-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)-9-methyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarboxaldehyde **5a**. Asymmetric unit of the crystal showing two molecules. Hydrogen atoms are omitted for clarity.

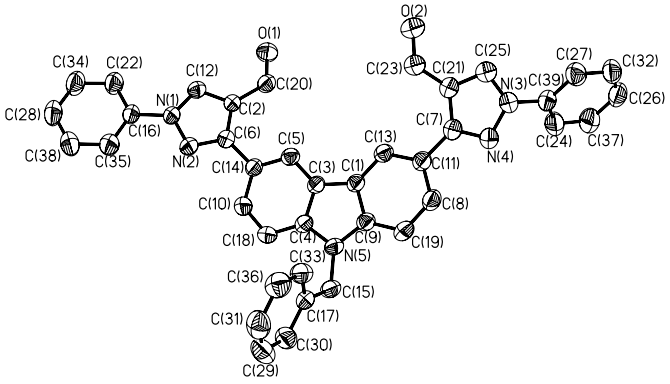
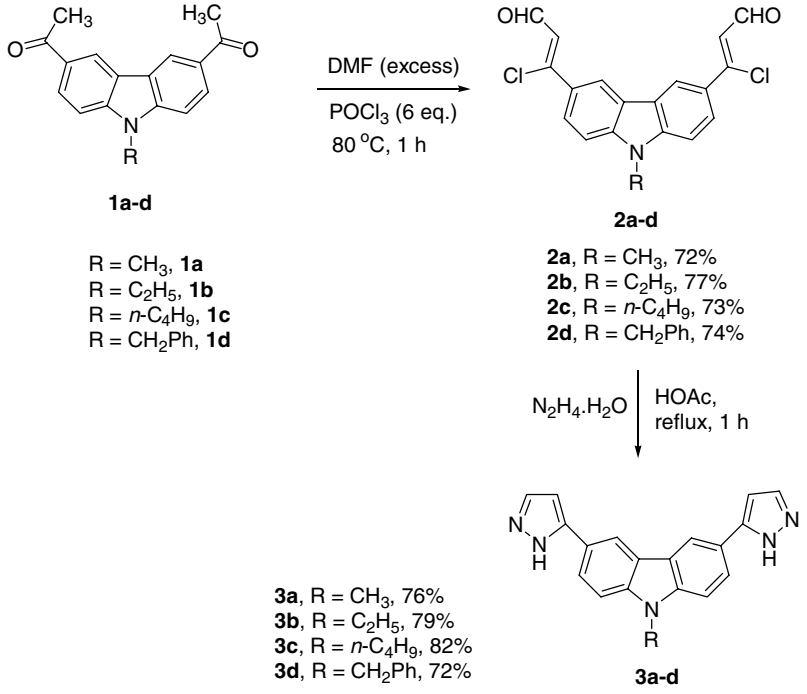


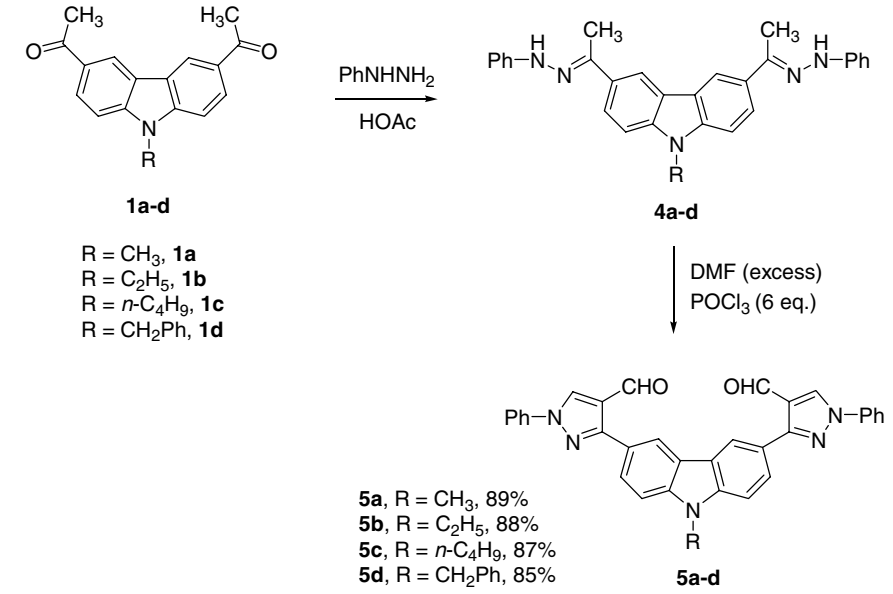
Figure 3. ORTEP diagram of 3-[6-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)-9-benzyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarboxaldehyde **5d**.



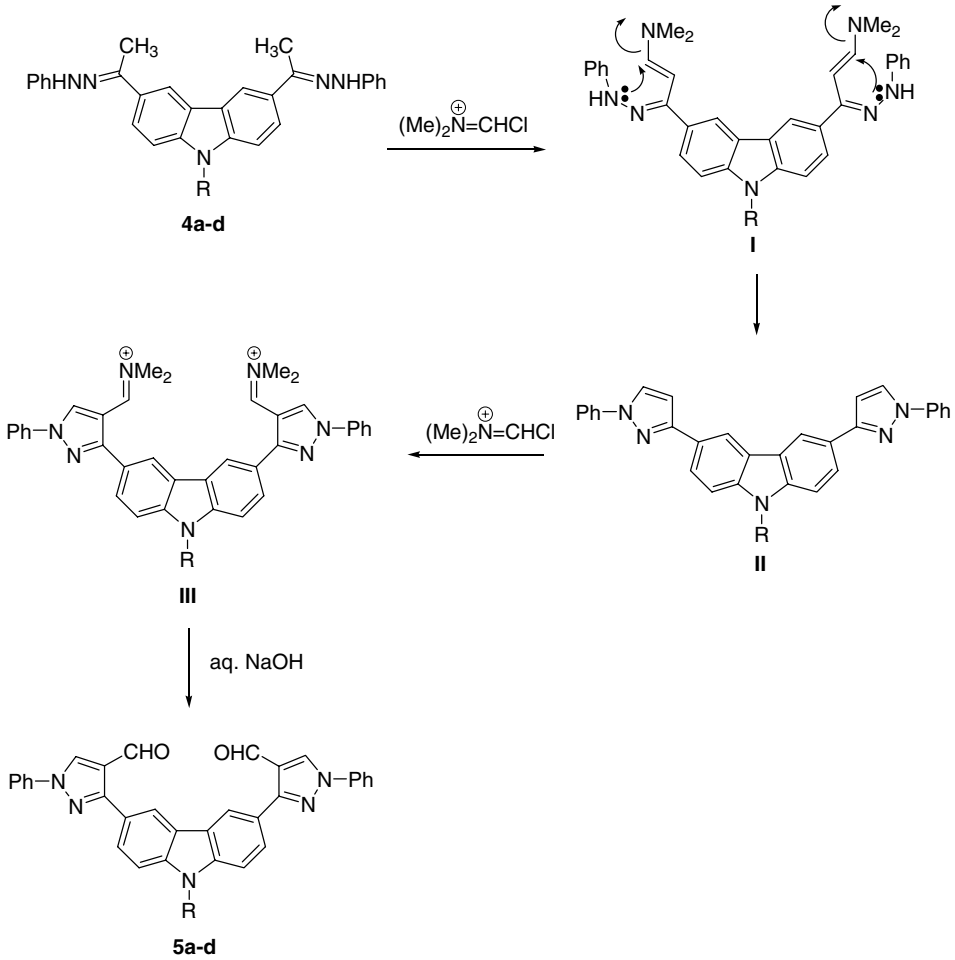
Scheme 1.

carbazolyl-β-chlorovinylaldehyde **2a** in 72% yield. Condensation followed by cyclization with hydrazine hydrate in acetic acid at reflux for 1 h gave dipyrazolylcarbazole **3a**[10] in 76% yield (Scheme 1).

The ^{1}H NMR spectrum of **2a** showed the aldehyde signal at $\delta \sim 10.11$ as a doublet ($J = 7.2$ Hz). The structure of product **2c** was also confirmed by the single crystal X-ray analysis.[11] The ^{1}H NMR spectrum of compound **3a**



Scheme 2.



Scheme 3.

showed the N–H signal at $\delta \sim 12.93$ as a broad singlet. The reaction also worked well for several other 9-alkyl carbazoles (Scheme 1).

The cyclization of iminium species under Vilsmeier conditions is an important synthetic tool in organic chemistry which provides entry to a large number of heterocyclic systems. The classical Vilsmeier–Haack reaction involves electrophilic substitution of an activated aromatic ring with a halomethyleneiminium salt to yield the corresponding iminium species.[12] However, the scope of this reagent is not restricted to aromatic formylation and a wide variety of alkene derivatives,[13] activated methyl and methylene groups[14] and oxygen and nitrogen nucleophiles[15] react with the Vilsmeier reagent to yield the corresponding iminium salts.

In connection with this, we describe the cyclization of phenylhydrazones of *N*-alkyl-3,6-diacetylcarbazoles under Vilsmeier–Haack reaction conditions. The hydrazones were easily prepared from the corresponding diacetylcarbazoles by the reaction with the phenylhydrazine in acetic acid at room temperature.[16]

Hydrazone **4a** of 9-methyl-3,6-diacetylcarbazole **1a** on reaction with an excess Vilsmeier reagent resulted in the formation of pyrazole dicarboxaldehyde **5a**[17] in 89% yield (Scheme 2). The reaction was also carried out with other 9-alkyl (ethyl, butyl and benzyl) substituents and the products were obtained in good yields. The structures of products **5a** and **5d** were also confirmed by the single crystal X-ray analysis.[18]

A possible mechanism for the formation of compounds **5a**–**d** is given in Scheme 3. The methyl group of phenylhydrazones **4a**–**d** reacts with the in situ generated halomethyleneiminium salt to form the intermediate **I** which loses a molecule of dimethylamine to yield pyrazole **II**. This further reacts with the halomethyleneiminium salt to afford iminium salt **III**, which is hydrolyzed to pyrazole dicarbaldehydes **5a**–**d**.

In summary, we have prepared an interesting class of heterocyclic compounds from easily available starting materials via a new synthetic procedure. The methods are simple and straightforward starting from easily accessible starting materials.

Acknowledgements

We thank DST and UPE for the financial support and DST for providing the single crystal X-ray diffractometer facility in our school. M.R. thanks the CSIR for a Junior Research Fellowship and Mr. P. Raghavaiah for his help in solving the crystal structures of the compounds.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.087.

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8. *General procedure*: the 9-alkyl-3,6-diacetylcarbazole (2 mmol) was dissolved in DMF (15 mL) at room temperature and then $POCl_3$ (12 mmol) was added dropwise at 0 °C. After a complete addition of $POCl_3$, the reaction mixture was warmed to room temperature and then heated at 80 °C for 1 h. The reaction mixture was poured onto crushed ice and then neutralized with a 10% aqueous NaOH solution. The product was extracted with DCM (3×30 mL) and then the extract washed with water (5–6 times) to remove excess DMF. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Finally, the crude material was purified by column chromatography. The 9-butyl substituted product gave light green colored, plate-shaped crystals from chloroform. 3-Chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-butyl-9*H*-carbazol-3-yl]-propenal **2c**: mp: 168 °C IR (KBr): 2959, 1660, 1586, 1482, 1389, 1241, 1167, 845, 791, 696 cm^{-1}; ^1H NMR (400 MHz, TMS, $CDCl_3$) δ: 10.26 (2H, d, $J = 6.8$ Hz, C*H*O), 8.60 (2H, s, ArC*H*-4/5), 7.91 (2H, dd, $J_1 = 1.6$ Hz, $J_2 = 1.72$ Hz, ArC*H*-1/8), 7.47 (2H, d, $J = 8.7$ Hz, ArC*H*-2/7), 6.79 (2H, d, $J = 6.8$ Hz, C=C*H*), 4.35 (2H, t, $J = 7.2$ Hz, N–CH_2), 1.92–1.85 (2H, m, N–CH$_2$–CH_2), 1.45–1.36 (2H, m, N–CH$_2$–CH$_2$–CH_2), 0.96 (3H, t, $J = 5.7$ Hz, CH_3); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 191.5 (*C*HO), 152.9, 143.0, 129.3, 127.3, 125.7, 123.1, 120.7, 109.6 (aromatic *C*), 43.5, 31.0, 20.5, 13.8 (*C*H$_3$); LC–MS: $m/z = 400$ (M+H$^+$) positive mode; Anal. Calcd for $C_{22}H_{19}Cl_2NO_2$: C, 66.01; H, 4.78; N, 3.50%. Found: C, 65.72; H, 4.85; N, 3.58%.
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10. *General procedure*: 3-Chloro-3-[6-(1-chloro-3-oxo-propenyl)-9-alkyl-9*H*-carbazol-3-yl]propenal (1.5 mmol) was dissolved in HOAc (20 mL) under reflux. The reaction mixture was cooled to room temperature and hydrazine

hydrate (7.5 mmol) was added slowly after which the reaction mixture was refluxed for 1 h. The reaction mixture was poured onto water and then neutralized with 10% aq $NaHCO_3$ solution. The compound was extracted with DCM (3×30 mL), the extract dried over anhyd Na_2SO_4 and the solvent was removed by distillation. 9-Methyl-3,6-di(1*H*-5-pyrazolyl)-9*H*-carbazole **3a**: mp: 152 °C; IR (KBr): 3180, 2962, 1713, 1603, 1444, 1338, 1261, 868, 798, 659 cm^{-1}; ^1H NMR (400 MHz, TMS, DMSO-d_6) δ: 12.93 (2H, br s, N*H*), 8.64 (2H, s, $J = 7.6$ Hz, ArC*H*-4/5), 7.95 (2H, d, $J = 8.3$ Hz, NH–C*H*), 7.72 (2H, s, ArC*H*-1/8), 7.63 (2H, d, $J = 8.5$ Hz, ArC*H*-2/7), 6.78 (2H, d, $J = 1.8$ Hz, NH–CH=C*H*), 3.91 (3H, s, CH_3); ^{13}C NMR (100 MHz, TMS, $CDCl_3$ + DMSO-d_6) δ: 148.5 (NH–*C*), 140.9 (N=*C*), 133.7 (N–*C*), 124.1 (Ar*C*-3), 123.7 (Ar*C*-4), 122.9 (Ar*C*-2), 117.4 (Ar*C*-1), 109.1 (ArC–4-*C*), 101.5 (HN–C=*C*), 29.4 (N–*C*H_3), LC–MS: $m/z = 312$ (M−H), negative mode; Anal. Calcd for $C_{19}H_{15}N_5$: C, 72.83; H, 4.82; N, 22.35%. Found: C, 72.72; H, 4.78; N, 22.52%.

11. The CCDC deposition number of 3-chloro-3-(6-(1-chloro-3-oxo-propenyl)-9-, butyl-9*H*-carbazol-3-yl)propenal **2c** is 612979; Formula: $C_{22}H_{19}Cl_2NO_2$, unit cell parameters: *a* 5.520(3), *b* 12.497(6), *c* 14.171(6), α 88.390(6), β 78.77, γ 81.705(9), space group P-1.
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16. The 9-alkyl-3,6-diacetylcarbazole (3.4 mmol) was dissolved in HOAc (20 mL) and then phenylhydrazine (7.1 mmol, 0.8 mL) was added slowly at rt. After stirring for 5 min at room temperature, a yellow colored solid precipitated which was separated by filtration. The crude product was washed with water and dried under vacuum (>85% yield). The hydrazones were sufficiently pure and were used without further purification.
17. *General procedure*: the phenylhydrazone (1.2 mmol) was dissolved in DMF (15 mL) and then $POCl_3$ (7.2 mmol) was added slowly dropwise at 0 °C. After a complete addition of $POCl_3$, the reaction mixture was heated at 90 °C for 1 h. The reaction mixture was poured onto crushed ice and then neutralized with 10% aq NaOH solution. The product was extracted with DCM (3×30 mL) and the organic layer was washed (5–6 times) with water to remove excess DMF. The DCM layer was dried over anhydrous Na_2SO_4 and evaporated. Finally, the crude material was purified by column chromatography. The 9-methyl substituted product was recrystallized from DCM as needle-shaped brown colored crystals and the 9-benzyl substituted product gave plate-shaped, brown colored crystals from hexane and ethyl acetate mixture. 3-[6-(4-Formyl-1-phenyl-1*H*-3-pyrazolyl)-9-methyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazole carboxaldehyde **5a**: mp: 132–133 °C; IR (KBr): 3113, 3052, 2976, 1733, 1674, 1537, 1384, 1130, 1025, 809 cm^{-1}; ^1H NMR (400 MHz, TMS, $CDCl_3$) δ: 10.18 (2H, s, C*H*O), 8.66 (2H, d, $J = 1.2$ Hz, C*H*=CHO), 8.60 (2H, s, ArC*H*-4/5), 8.03 (1H, d, $J = 1.6$ Hz, ArC*H*-1), 8.01 (1H, d, $J = 1.60$ Hz, ArC*H*-8), 7.89 (2H, s, ArC*H*-2/6), 7.87 (2H, s, ArC–*H*), 7.58–7.53 (6H, m, ArC–*H*), 7.44 (2H, t, $J = 7.4$ Hz, ArC–*H*), 3.98 (3H, s, CH_3); ^{13}C NMR (100 MHz, TMS, $CDCl_3$) δ: 185.5 (Ar*C*=O), 155.0, 141.9, 139.1, 131.2, 129.6, 127.7, 127.2, 123.1, 122.6, 122.4, 121.2, 119.6, 108.8 (Ar-*C*), 29.3 (aliphatic *C*); LC–MS: $m/z = 522$ ($M+H^+$) positive mode; Anal. Calcd for $C_{33}H_{23}N_5O_2$: C, 75.99; H, 4.44; N, 13.43%. Found: C, 76.16; H, 4.33; N, 13.51%.
18. The CCDC deposition number of 3-[6-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)-9-methyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarboxaldehyde **5a** is 612980; formula: $C_{33}H_{23}N_5O_2$; unit cell parameters: *a* 21.036(3), *b* 9.9409(14), *c* 24.623(4), β 91.715(3) space group P2(1)/n. The CCDC deposition number of 3-[6-(4-formyl-1-phenyl-1*H*-3-pyrazolyl)-9-benzyl-9*H*-3-carbazolyl]-1-phenyl-1*H*-4-pyrazolecarbaldehyde **5d** is 612978; formula: $C_{39}H_{27}N_5O_2$; unit cell parameters: *a* 10.5420(11), *b* 11.7232(13), *c* 12.8321(14), α 80.861(2), β 75.235(2), γ 77.600(2), space group P-1.