A New Versatile Route to the Synthesis of a Novel Series of Highly Substituted 1,1′-Carbonylbispyrazole Derivatives

Sattar Saberi,[a] Hossein Eshghi,*[a] Mohamad Rahimizadeh,[a] Khalil Abnous[b]

[a] Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, 91775-1436 Mashhad, Iran
E-mail: heshghi@um.ac.ir; E-mail: satar.saberi@gmail.com; Fax +98(511)8795457

[b] Pharmaceutical Research Center, Department of Medicinal Chemistry, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Received: 05.12.2013; Accepted after revision: 15.01.2014

Abstract: The reaction of 1*H*-pyrazole-1-carbohydrazide with various α,β-unsaturated nitriles under suitable conditions leads to a cyclocondensation reaction, thereby providing a novel route for the synthesis of a series of highly substituted 1,1′-carbonylbispyrazole derivatives.

Key words: 1*H*-pyrazole-1-carbohydrazide, pyrazoles, α,β-unsaturated nitriles, carbonylbispyrazoles, cyclizations, heterocycles

Pyrazoles have attracted significant interest among the azole family due to their diverse therapeutic potential for anticancer,[1] antifungal,[2] antimicrobial,[3] and osteogenesis treatment.[4] The pyrazole moiety is the main pharmacophore in the established anti-inflammatory drugs, celecoxib[5] and SC-558[6] (**A** and **B**, Figure 1). The recent success of functionalized pyrazole derivatives as cannabinoid-1 (CB1) receptor antagonists,[7] kinase inhibitors, and σ_1 receptor antagonists[8] has further highlighted the importance of this heterocycle in medicinal chemistry.[9]

A survey of the literature revealed that few reports deal with the synthesis of the pyrazole ring linked to another pyrazole. Synthetic routes to obtain these compounds and studies on their potential as pharmaceuticals and agrochemicals have been relatively little explored.[10–12] The synthesis of bispyrazoles and their application as heteroscorpionate precursor ligands in organometallic and bioinorganic chemistry has been investigated in recent years.[13,14] In addition, some authors[15] have reported bispyrazole derivatives capable of capturing oxygen and free radicals in vivo.[15] Some bispyrazoles have found application as antitumor agents (**C** and **D**, Figure 1).[16]

1,1′-Carbonylbispyrazoles have been most commonly synthesized by a substitution reaction involving phosgene and other derivatives with pyrazoles.[17–24] However, this synthetic procedure is efficient only when the starting materials are symmetrically substituted or unsubstituted pyrazoles, because unsymmetrical 3- or 5-substituted pyrazoles may exist in two tautomeric structures in solution and their N-1-substitution reactions could lead to three possible carbonyl-bispyrazoles isomers. More recently, Bonacorso reported the synthesis of carbonylbispyrazoles prepared by the reaction of 4-methoxy-4-aryl(heteroaryl)-1,1,1-trihalobut-3-en-2-ones with 1,3-diaminoguanidine monohydrochloride in ethanol and water as solvents.[25]

We now wish to report an approach to the synthesis of highly substituted 1,1′-carbonylbispyrazole derivatives **5a**–**f** (Scheme 2) based on the retrosynthetic analysis outlined in Scheme 1. To the best of our knowledge, this multistep reaction for 1,1′-carbonylbispyrazoles is unprecedented.

The target compounds were synthesized according to the steps outlined in Scheme 2. The key intermediates **2a** and **2b** were synthesized by condensation of the commercially available hydrazine carboxylic acid ethyl ester **1** with the synthesized α,β-unsaturated nitriles **4a**,**b**.[26] Treatment of the pyrazole derivatives **2a**,**b** with four equivalents of hydrazine hydrate led to pyrazole derivatives **3a**,**b** contain-

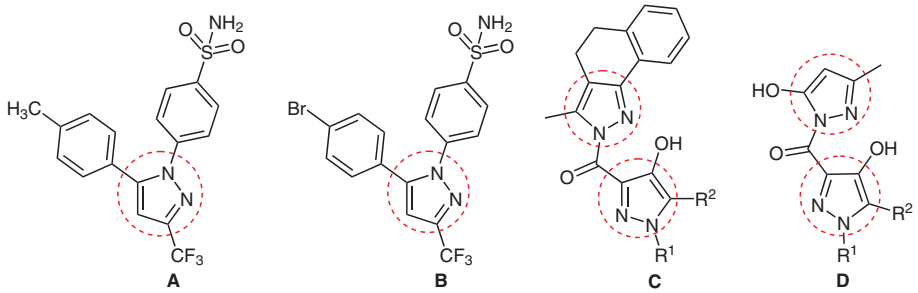
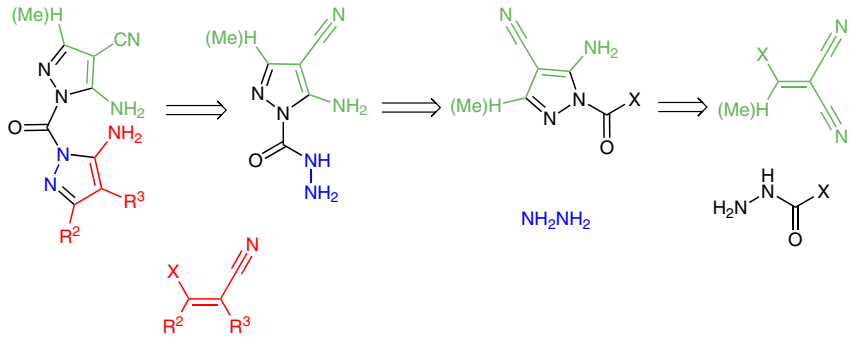


Figure 1 Scaffolds **A**–**D**

SYNLETT 2014, 25, 0889–0893
Advanced online publication: 14.02.2014
DOI: 10.1055/s-0033-1340737; Art ID: ST-2013-D1113-L



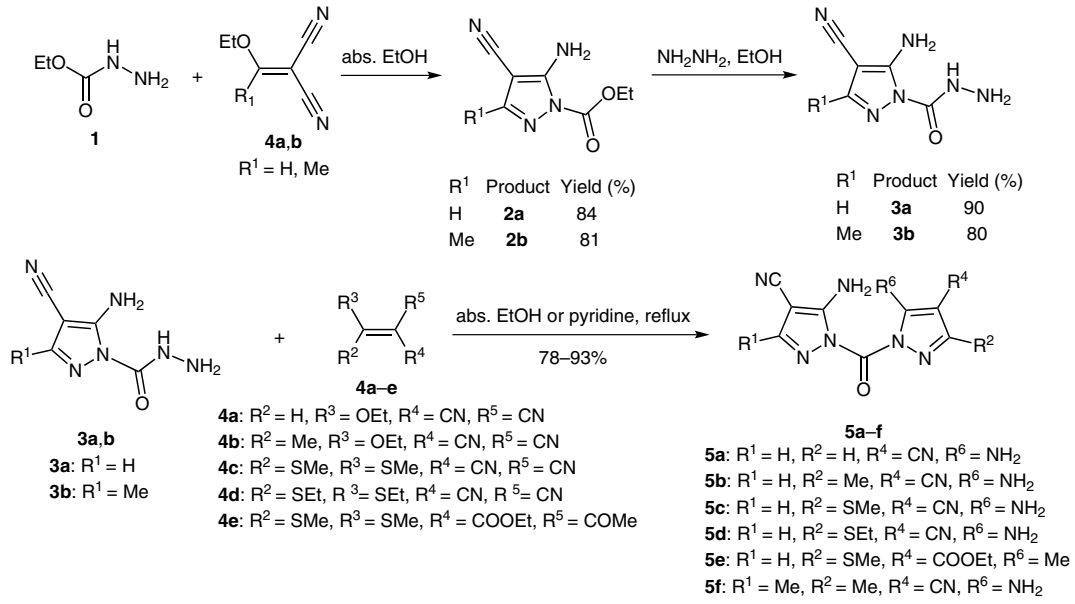
Scheme 1 Retrosynthetic analysis of highly substituted series of 1,1′-carbonylbispyrazole derivatives

ing a carbohydrazide moiety in 90% and 80% yield, respectively.[27] The structures of **3a**,**b** were supported by FTIR and ^{1}H NMR spectroscopy and elemental analysis. For example, the IR spectrum of **3a** showed absorption bands at 3416–3178, 2238, and 1646 cm^{-1} indicating the presence of NH_2 and NH, cyano and C=O groups, respectively. The ^{1}H NMR spectrum of **3a** showed a signal at δ = 7.72 ppm corresponding to azomethine proton (N=CH). Furthermore, the disappearance of the characteristic pattern of the ethoxy group in addition to the presence of two singlets corresponding to two NH_2 and NH protons at δ = 6.82 and 12.09 ppm confirmed the structure of the product.

Condensation of the 1*H*-pyrazole-1-carbohydrazide derivatives **3a**,**b** with different α,β-unsaturated nitrile derivatives **4a**–**e**[28–33] in the appropriate refluxing solvent furnished the novel series of 1,1′-carbonylbispyrazole derivatives **5a**–**f** in good to excellent yields (78–93%).[34,35]

The structural assignment of compounds **5a**–**f** was based on spectroscopic and microanalytical data. For example, the IR spectrum of **5b** revealed the presence of an additional cyano band at 2220 cm^{-1}. The ^{1}H NMR spectrum of **5b** showed the presence of two signals at δ = 2.52 and 8.67 ppm corresponding to the methyl group and the pyrazolyl proton, respectively. Whereas the ^{1}H NMR spectrum of the precursor **3a** showed the signals corresponding to NH_2 and NH at δ = 6.82 and 12.09 ppm, respectively, which disappeared upon addition of D_2O, the ^{1}H NMR spectrum of the cyclized product **5b** did not show these resonances. Instead, an exchangeable broad singlet at δ = 9.23 ppm in DMSO-d_6 confirmed that heterocyclization had occurred. The ^{13}C NMR spectrum of **5b** revealed the appearance of two signals at δ = 113.9 and 115.5 ppm, attributed to the two cyano groups confirming that heterocyclization with the α,β-unsaturated nitrile **2b** had occurred. The carbonyl carbon interfacing the two pyrazole rings of **5b** appeared as a resonance at δ = 164.6 ppm.

The reaction of **3a**,**b** with α,β-unsaturated nitrile derivatives was studied under different conditions and optimal conditions for the preparation of **5a**,**b** were achieved by refluxing the reaction mixture in ethanol. Other compounds **5** were prepared in high yield by refluxing the reactants in pyridine.



1

4a,**b**
R^1 = H, Me

3a,**b**
3a: R^1 = H
3b: R^1 = Me

4a–e
4a: R^2 = H, R^3 = OEt, R^4 = CN, R^5 = CN
4b: R^2 = Me, R^3 = OEt, R^4 = CN, R^5 = CN
4c: R^2 = SMe, R^3 = SMe, R^4 = CN, R^5 = CN
4d: R^2 = SEt, R^3 = SEt, R^4 = CN, R^5 = CN
4e: R^2 = SMe, R^3 = SMe, R^4 = COOEt, R^5 = COMe

5a–f
5a: R^1 = H, R^2 = H, R^4 = CN, R^6 = NH_2
5b: R^1 = H, R^2 = Me, R^4 = CN, R^6 = NH_2
5c: R^1 = H, R^2 = SMe, R^4 = CN, R^6 = NH_2
5d: R^1 = H, R^2 = SEt, R^4 = CN, R^6 = NH_2
5e: R^1 = H, R^2 = SMe, R^4 = COOEt, R^6 = Me
5f: R^1 = Me, R^2 = Me, R^4 = CN, R^6 = NH_2

Scheme 2 Procedure to construct fully substitute 1,1′-carbonylbispyrazole derivatives **5a**–**f**

^{1}H and ^{13}C chemical shifts of compounds **5a–c,f** are shown in Figure 2.

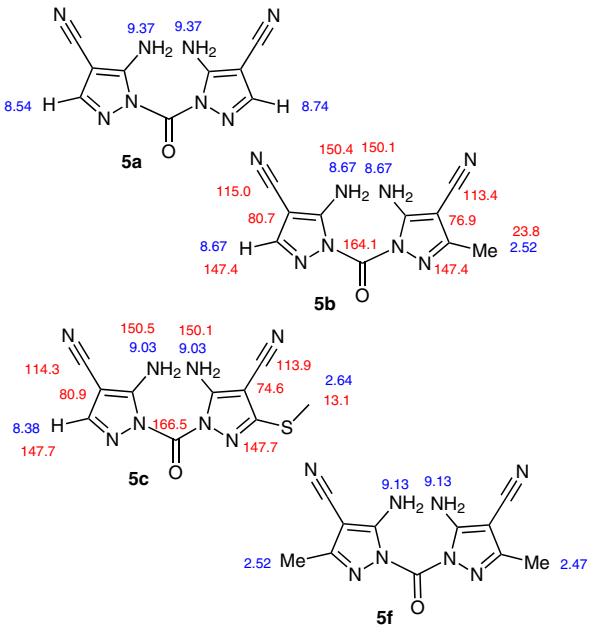
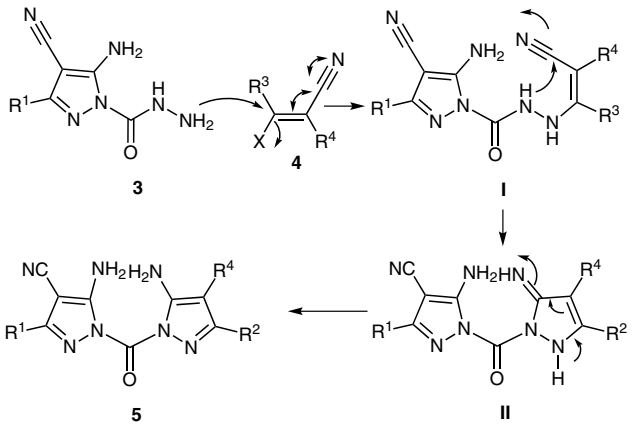


Figure 2 ^{1}H NMR and ^{13}C NMR spectroscopic assignment of **5a–c,f**

A suggested mechanism for the formation of **5** is depicted in Scheme 3. Assembly of the pyrazole ring is envisaged to occur by intramolecular heterocyclization of intermediate **I**, which arises from precursor **3** by conjugate addition to **4** followed by aromatization to form the pyrazole ring.



Scheme 3 Postulated mechanism for formation of 1,1′-carbonylbispyrazole derivatives

In conclusion, a general and scalable procedure has been successfully developed to synthesize 5-amino-4-cyano-1*H*-pyrazole-1-carbohydrazides and 5-amino-4-cyano-3-methyl-1*H*-pyrazole-1-carbohydrazides as novel precursors using inexpensive starting materials, via the reaction with α,β-unsaturated nitriles to obtain a large variety of highly substituted 1,1′-carbonyl-bispyrazole derivatives. All 1,1′-carbonylbispyrazoles described herein are new chemical entities and it would be difficult to synthesize them by alternative methods.[17–25] This procedure affords the products in good to excellent yields, requiring short reaction times and a simple workup. A wide range of α,β-unsaturated compounds has been tested, suggesting that this method can be used to synthesize a large variety of highly substituted 1,1′-carbonylbispyrazoles. The route described herein may open the door to various substitutions and transformations to access to libraries of biologically active heterocyclic compounds.

Acknowledgment

We are grateful to the Department of Chemistry, Ferdowsi University of Mashhad, Iran for financial Support (Grant No. 3/15421).

References and Notes

(1) Vujasinovic, I.; Paravic, A.; Mlinaric, M. K.; Brajsa, K.; Bertosa, B. *Bioorg. Med. Chem.* **2012**, *20*, 2101.
(2) Zhang, C. Y.; Liu, X. H.; Wang, B. L.; Wang, S. H.; Li, Z. M. *Chem. Biol. Drug Des.* **2010**, *75*, 489.
(3) Gadakh, A. V.; Pandit, C.; Rindhe, S. S.; Karale, B. K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5572.
(4) Lv, H. S.; Han, Q. Q.; Ding, X. L.; Zhou, J. L.; Yang, P. S.; Miao, J. Y.; Zhao, B. X. *Arch. Pharm.* **2012**, *345*, 870.
(5) Bing, R. J.; Lomnicka, M. *J. Am. Coll. Cardiol.* **2002**, *39*, 521.
(6) Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C. *Nature (London)* **1996**, *384*, 644.
(7) (a) Seo, H. J.; Kim, M. J.; Lee, S. H.; Lee, S. H.; Kim, M. E.; Kim, J.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 1149. (b) Yan, L.; Huo, P.; Debenham, J. S.; Madsen-Duggan, C. B.; Lao, J.; Chen, R. Z.; Xiao, J. C.; Shen, C. P.; Stribling, D. S.; Shearman, L. P.; Strack, A. M.; Tsou, N.; Ball, R. G.; Wang, J. X.; Tong, T.; Bateman, T. J.; Reddy, V. B. G.; Fong, T. M.; Hale, J. J. *J. Med. Chem.* **2010**, *53*, 4028.
(8) (a) Cho, Y. S.; Borland, M.; Brain, C.; Chen, C. H.-T.; Cheng, H.; Chopra, R.; Chung, K.; Groarke, J.; He, G.; Hou, Y.; Kim, S.; Kovats, S.; Lu, Y.; O'Reilly, M.; Shen, J.; Smith, T.; Trakshel, G.; Vögtle, M.; Xu, M.; Sung, M. J. *J. Med. Chem.* **2010**, *53*, 7938. (b) Howard, S.; Berdini, V.; Boulstridge, J. A.; Carr, M. G.; Cross, D. M.; Curry, J.; Devine, L. A.; Early, T. R.; Fazal, L.; Gill, A. L.; Heathcote, M.; Maman, S.; Matthews, J. E.; McMenamin, R. L.; Navarro, E. F.; O'Brien, M. A.; O'Reilly, M.; Rees, D. C.; Reule, M.; Tisi, D.; Williams, G.; Vinkovic, M.; Wyatt, P. G. *J. Med. Chem.* **2009**, *52*, 379. (c) Diaz, J. L.; Cuberes, R.; Berrocal, J.; Contijoch, M.; Christmann, U.; Fernández, A.; Port, A.; Holenz, J.; Buschmann, H.; Laggner, C.; Serafini, M. T.; Burgueno, J.; Zamanillo, D.; Merlos, M.; Vela, J. M.; Almansa, C. *J. Med. Chem.* **2012**, *55*, 8211.
(9) For recent pyrazole syntheses, see for example: (a) Jones Raymond, C. F.; Seager Laura, E.; Elsegood Mark, R. J. *Synlett* **2011**, 211. (b) Vijesh, A. M.; Isloor, A. M.; Shetty, P.; Sundershan, S.; Fun, H. K. *Eur. J. Med. Chem.* **2013**, *62*, 410. (c) Jiang, J.; Du, C.; Gu, C.; Ji, Y. *Synlett* **2012**, *23*, 2965. (d) Aly, H. M.; El-Gazzar, M. G. *Arzneim. Forsch.* **2012**, *62*, 105. (e) Adib, M.; Mohammadi, B.; Bijanzadeh, H. *Synlett* **2008**, 3180. (f) Morrill, C.; Babu, S.; Almstead, N. G.; Moon, Y. *Synthesis* **2013**, *45*, 1791. (g) Reddy, H. R.; Vijaykumar, J.; Gree, R. *Synthesis* **2013**, *45*, 830. (h) Janin, Y. L. *Org. Chem.* **2010**, *7*, 314. (i) Siegmund, A.; Retz, D.; Xi, N.; Dominguez, C.; Burli, R.; Liu, L. *Synlett* **2008**, 1005.

(j) Willy, B.; Mouller, T. J. *J. Org. Lett.* **2011**, *13*, 2082. (k) Rosa, A.; Machado, P.; Vargas, S.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Synlett* **2008**, 1673.

(10) (a) Denisova, A. B.; Sosnovskikh, V. Y.; Dehaen, W.; Toppet, S.; Meervelt, L. V.; Bakulev, V. A. *J. Fluorine Chem.* **2002**, *115*, 183. (b) Shawali, A. S.; Sherif, S. M.; El-Merzabani, M. M.; Darwish, M. A. A. *J. Heterocycl. Chem.* **2009**, *46*, 548.

(11) Hanamoto, T.; Hakoshima, Y.; Egashira, M. *Tetrahedron Lett.* **2004**, *45*, 7573.

(12) Angerman, A.; Franke, H.; Geisler, J.; Johann, G.; Rees, R. US 4008200, **1991**.

(13) Hoffmann, A.; Flörke, U.; Schürmann, M.; Herres-Pawlis, S. *Eur. J. Org. Chem.* **2010**, 4136.

(14) Otero, A.; Fernandez-Baeza, J.; Lara-Sanchez, A.; Tejeda, J.; Sanchez-Barba, L. F. *Eur. J. Inorg. Chem.* **2008**, 5309.

(15) Heitaro, O.; Takashi, I.; Kazuhisa, S.; Tetsuo, O. US 612130519, **2000**.

(16) (a) Rostom, S. A. F. *Bioorg. Med. Chem.* **2010**, *18*, 2767. (b) Francisco, M. E. Y.; Seltzman, H. H.; Gilliam, A. F.; Mitchell, R. A.; Rider, S. L.; Pertwee, R. G.; Stevenson, L. A.; Thomas, B. F. *J. Med. Chem.* **2002**, *45*, 2708.

(17) Soliman, R.; Darwish, S. A. S. *J. Med. Chem.* **1983**, *11*, 1959.

(18) Sheludyakov, V. D.; Shedulyakova, S. V.; Kuznetsova, M. G.; Silkina, N. N.; Mironov, V. F. *Zh. Obshch. Khim.* **1980**, *4*, 875.

(19) Scherer, J.; Klausener, A.; Soellner, R. DE 10035011, **2002**.

(20) Esteves-Souza, A.; Echevarrıa, A.; Vencato, I.; Jimeno, M. L.; Elguero, J. *Tetrahedron* **2001**, *57*, 6147.

(21) Byers, P. K.; Canty, A. J.; Honeyman, R. T.; Gardinier, J. R.; Reger, D. L. *Inorg Synth.* **2004**, *34*, 30.

(22) Tang, L.; Jia, W.; Wang, Z.; Wang, H. *J. Organomet. Chem.* **2002**, *649*, 152.

(23) Katritsky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Vol. 3; Elsevier Science: New York, **1996**.

(24) Safaei, S.; Mohammadpoor-Baltork, I.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Khavasi, H. R. *Synlett* **2013**, *24*, 1086.

(25) Bonacorso, H. G.; Cechinel, C. A.; Porte, L. M. F.; Navarini, J.; Cavinatto, S. R.; Sehnem, C.; Martins, D. B.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **2010**, *47*, 1073.

(26) **General Procedure for the Synthesis of Pyrazoles 2**
A mixture of **4** (82 mmol) and hydrazinecarboxylic acid ethyl ester (**1**, 8.52 g, 81 mmol) was stirred under reflux in abs. EtOH (120 mL) for 4 h. After cooling in the refrigerator overnight, the precipitate was filtered and washed with cold Et_2O to afford **2** as colorless needles.
Ethyl 5-Amino-4-cyano-1*H*-pyrazole-1-carboxylate (2a)
Yield 12.4 g (84%); mp 165–167 °C. IR: ν_{max} = 3493, 3280, 3214, 3128–3156, 2219, 1771, 1628 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$): δ = 1.48 (t, 3 H, CH_3), 4.54 (q, 2 H, CH_2), 6.32 (s, 2 H, NH_2), 7.57 (s, 1 H, CH).
Ethyl 5-Amino-4-cyano-3-methyl-1*H*-pyrazole-1-carboxylate (2b)
Yield 12.7 g (81%); mp 180–181 °C. IR: ν_{max} = 3406, 3320, 3247, 2990, 2213, 1736, 1646, 1563, 1471, 1332, 1256, 1021 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$): δ = 1.43 (t, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 4.48 (q, 2 H, CH_2), 6.48 (s, 2 H, NH_2). Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.38; H, 5.11; N, 28.78.

(27) **General Procedure for the Synthesis of 1*H*-Pyrazole-1-carbohydrazides 3**
Hydrazine monohydrate (10 mL, 206 mmol) was added to a solution of **2** (55 mmol) in abs. EtOH (60 mL), and the mixture was refluxed for 3 h. The excess of solvent was distilled off, and the crude product obtained was poured into ice water. After cooling in the refrigerator overnight, the solid residue was filtered and washed with cold water and dried to give **3** as a white solid.
5-Amino-4-cyano-1*H*-pyrazole-1-carbohydrazide (3a)
Yield 8.2 g (90%); mp 175 °C. IR: ν_{max} = 3416, 3341, 3284, 3240, 3178, 2956, 2238, 1646, 1570, 1034 cm^{-1}. ^1H NMR (100 MHz, DMSO-d_6): δ = 6.82 (s, 4 H, 2 NH_2), 7.72 (s, 1 H, CH), 12.09 (s, 1 H, NH). Anal. Calcd for $C_5H_6N_6O$: C, 36.15; H, 3.64; N, 50.58. Found: C, 36.08; H, 3.58; N, 50.49.
5-Amino-4-cyano-3-methyl-1*H*-pyrazole-1-carbohydrazide (3b)
Yield 7.9g (80%); mp 125–127 °C. IR: ν_{max} = 3403, 3341, 3284, 3242, 2994, 2217, 1660, 1298 cm^{-1}. ^1H NMR (100 MHz, CD_3COCD_3): δ = 2.20 (s, 3 H, CH_3), 5.35 (s, 4 H, 2 NH_2), 11.19 (s, 1 H, NH). Anal. Calcd for $C_6H_8N_6O$: C, 40.00; H, 4.48; N, 46.65. Found: C, 39.01; H, 4.41; N, 46.60.

(28) Dooley, M. J.; Quinn, R. J.; Scammells, P. J. *Aust. J. Chem.* **1989**, *42*, 747.

(29) Ferlin, M.; Grazia, M. B.; Valerio, D. A. *Tetrahedron* **2006**, *62*, 6222.

(30) Thomae, D.; Perspicace, E.; Henryon, D.; Xu, Z.; Hesse, S.; Kirsch, G.; Schneider, S.; Seck, P. *Tetrahedron* **2009**, *65*, 10453.

(31) Amico, J. J.; Ruminski, P. G.; Suba, L. A.; Freeman, J. J.; Dahl, W. E. *Phosphorus Sulfur Relat. Elem.* **1985**, *21*, 307.

(32) Wu, Y.; Li, H.; Yang, H. *Org. Biomol. Chem.* **2010**, *8*, 3394.

(33) Liang, D.; Wang, M.; Bekturhun, B.; Xiong, B.; Liu, Q. *Adv. Synth. Catal.* **2010**, *352*, 1593.

(34) **Synthesis of 1,1′-Carbonylbis(5-amino-1*H*-pyrazole-4-carbonitrile) (5a)**
Compound **4a** (0.62 g, 5 mmol) was added to a stirring solution of **3a** (0.82 g, 5 mmol) in EtOH (10 mL). The contents were stirred at r.t. for a further 30 min and then refluxed for 3 h. After the completion of the reaction [monitoring by TLC using $CHCl_3$–MeOH (4:1, v:v) as eluent], the white solid was filtered under suction and washed with cold EtOH (1.1g, 93%); mp >300 °C (dec.). IR: ν_{max} = 3321, 3277, 3126, 2235, 1688, 1610, 1570, 1487, 1338, 1329, 1262 cm^{-1}. ^1H NMR (100 MHz, DMSO-d_6): δ = 8.54 (s, 1 H, arom.), 8.72 (s, 1 H, arom.), 9.37 (br, 4 H, NH_2, D_2O exchangeable). Anal. Calcd for $C_9H_6N_8O$: C, 44.63; H, 2.50; N, 46.27. Found: C, 44.54; H, 2.55; N, 46.12.
Synthesis of 5-Amino-1-(5-amino-4-cyano-1*H*-pyrazole-1-carbonyl)-3-methyl-1*H*-pyrazole-4-carbonitrile (5b)
Compounds **4b** (0.54 g, 4 mmol) and **3a** (0.66 g, 4 mmol) were added to a solution of Na of NaOEt prepared by adding (0.21 g, 9 mmol) to abs. EtOH (10 mL). The mixture was stirred at r.t. for 30 min and then heated to reflux for 3 h. After the completion of the reaction [monitoring by TLC using $CHCl_3$–MeOH (3:1, v/v) as eluent], the mixture was cooled to r.t. H_2O (5 mL) was added, and the mixture was neutralized by HCl. The collected solid was recrystallized from MeOH (0.81 g, 81%); mp >300 °C (dec.). IR: ν_{max} = 3340, 3310, 3248, 3180, 3116, 2232, 2221, 1650, 1594 cm^{-1}. ^1H NMR (100 MHz, DMSO-d_6): δ = 2.52 (s, 3 H, CH_3), 8.67 (s, 1 H, arom.), 9.25 (br, 4 H, NH_2, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.3, 77.4, 81.1, 113.9, 115.5, 147.9,150.6, 150.9, 164.6. Anal. Calcd for $C_{10}H_8N_8O$: C, 46.88; H, 3.15; N, 43.73. Found: C, 46.78; H, 3.04; N, 43.60.

(35) **General Procedure for the Synthesis of 1,1′-Carbonylbispyrazole Derivatives 5c–f**
A mixture of of **4c–e** (4 mmol) and **3** (4 mmol) in pyridin (5 mL) was heated to reflux for 4 h, then poured onto ice water and the mixture neutralized with concd HCl. The precipitated solid was filtered, washed with H_2O, and crystallized from an appropriate solvent.

5-Amino-1-(5-amino-4-cyano-1*H*-pyrazole-1-carbonyl)-3-(methylthio)-1*H*-pyrazole-4-carbonitrile (5c)
Yield 0.89 g (78%, DMF); mp >300 °C. IR: ν_{max} = 3353, 3304, 3027, 3186, 2240, 2218, 1659, 1607, 1567, 1384, 1342, 1291 cm^{-1}. ^1H NMR (100 MHz, DMSO-d_6): δ = 2.64 (s, 3 H, SCH_3), 8.37 (s, 1 H, arom.), 9.03 (br, 4 H, NH_2, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.2, 74.6, 80.9, 113.9, 114.3, 147.7, 150.1, 150.4, 166.5. Anal. Calcd for $C_{10}H_8N_8OS$: C, 41.66; H, 2.80; N, 38.87; S, 11.12. Found: C, 41.56; H, 2.46; N, 38.57; S, 11.04.

5-Amino-1-[4-amino-5-cyano-3-(ethylthio)-1*H*-pyrazole-1-carbonyl]-1*H*-pyrazole-4-carbonitrile (5d)
Yield 1.05g (87%, EtOH); mp >300 °C (dec.). IR: ν_{max} = 3350, 3320, 3252, 3187, 3101, 2994, 2941, 2217, 1657, 1597, 1563, 1534, 1465, 1380, 1339, 1286, 1248 cm^{-1}. ^1H NMR (100 MHz, DMSO-d_6): δ = 1.26–1.41 (t, 3 H, SCH_2CH_3), 3.11–3.30 (q, 2 H, SCH_2CH_3), 8.62 (s, 1 H, arom.), 9.19 (br, 4 H, NH_2, D_2O exchangeable). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.7, 25.8, 75.8, 81.9, 115.3, 148.8, 151.4, 151.6, 167.2. Anal. Calcd for $C_{11}H_{10}N_8OS$: C, 43.70; H, 3.33; N, 37.07; S, 10.61. Found: C, 51.64; H, 3.29; N, 37.42; S, 10.55.

Ethyl 1-(5-Amino-4-cyano-1*H*-pyrazole-1-carbonyl)-5-methyl-3-(methylthio)-1*H*-pyrazole-4-carboxylate (5e)
Yield 1.09g (82%, *n*-hexane); mp 128–129 °C. IR: ν_{max} = 3351, 3313, 3250, 3219, 3184, 2239, 2217, 1658, 1607, 1566, 1534, 1462, 1384, 1342, 1278 cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$): δ = 1.38–1.52 (t, 3 H, OCH_2CH_3), 2.65 (s, 3 H, CH_3), 2.88 (s, 3 H, SCH_3), 4.33–4.56 (q, 2 H, OCH_2CH_3), 8.29 (s, 1 H, arom.). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.1, 14.2, 15.3, 62.8, 81.9, 112.9, 115.4, 146.6, 147.4, 149.0, 164.1, 164.6. Anal. Calcd for $C_{13}H_{14}N_6O_3S$: C, 46.70; H, 4.22; N, 25.14; S, 9.59. Found: C, 46.62; H, 4.15; N, 25.09; S, 9.59.

5-Amino-1-(4-amino-5-cyano-3-methyl-1*H*-pyrazole-1-carbonyl)-1*H*-pyrazole-4-carbonitrile (5f)
Yield 0.87g (81%, MeOH). IR: ν_{max} = 3327, 3277, 3120, 2234, 1680, 1609, 1565, 1485, 1335 cm^{-1}. ^1H NMR (100 MHz, DMSO-d_6): δ = 2.47 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3), 9.13 (br, 4 H, 2 NH_2, D_2O exchangeable). ^1H NMR (100 MHz, CD_3COCD_3): δ = 2.49 (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 8.40 (br, 4 H, 2 NH_2, D_2O exchangeable). Anal. Calcd for $C_{11}H_{10}N_8O$: C, 48.89; H, 3.73; N, 41.46. Found: C, 48.81; H, 3.69; N, 41.40.