ORGANIC LETTERS

2009
Vol. 11, No. 22
5290−5293

Pyrazolo[3,4-*d*]pyrimidinophanes: Convenient Synthesis of a New Class of Cyclophane and X-ray Structure of the First Representative†

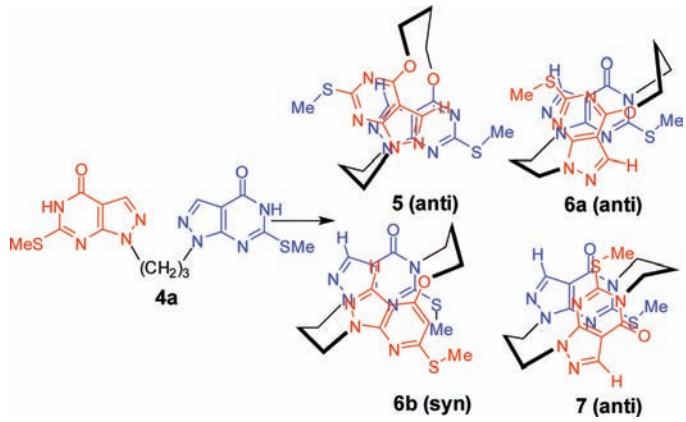
Kamlakar Avasthi,*,‡ Amantullah Ansari,‡ Ashish K. Tewari,‡ Ruchir Kant,§ and Prakas R. Maulik§

Medicinal and Process Chemistry Division and Molecular and Structural Biology Division, Central Drug Research Institute, CSIR, Lucknow 226001, India

kavasthi@rediffmail.com

Received September 30, 2009

ABSTRACT



A convenient synthesis of a new class of novel pyrazolo[3,4-*d*]pyrimidinophanes (four products, 41%), a new class of cyclophane, and X-ray structure of the first dissymmetrical [3.4]pyrazolo[3,4-*d*]pyrimidinophane (22%) are reported for the first time. The conformation of major *syn* product 6b is stabilized by weak $\pi-\pi$ and O···Ar interactions.

In the course of our studies on flexible 1,3-bis(4,6-dimethylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propane (**1a**, Figure 1) by ^{1}H NMR in solution[1a] and X-ray crystallography in solid,[1b] we discovered the potential of the pyrazolo[3,4-*d*]pyrimidine core, which is isomeric with the biologically important purine system, for studying arene interactions at both the molecular and supramolecular level.

Since then robustness of the unusual U-motif formed as a result of intramolecular arene interaction in **1a** has been established in many more symmetrical (**1**)[1c−h] and two dissymmetrical compounds (**2**[1i] and **3**,[1j] Figure 1) both by ^{1}H NMR in solution and X-ray crystallography in solid, except for **1h**,[1g] which shows a different conformation (normal U-motif) compared to all other 14 propylene linker compounds showing unusual U-motif due to intramolecular arene interaction.

More surprisingly, structurally quite different compounds (**4b**−**4d**, Figure 1) derived from **1a** via intermediate **4a**[1k] also show intramolecular arene interaction both by ^{1}H NMR in solution and X-ray crystallography in solid.[1l−n] Vogtle refers to singly linked molecules that adopt π-stacked conformations as "protophanes".[2]

† C.D.R.I. Communication No. 7836.
‡ Medicinal and Process Chemistry Division.
§ Molecular and Structural Biology Division.

10.1021/ol902264t CCC: $40.75
Published on Web 10/29/2009

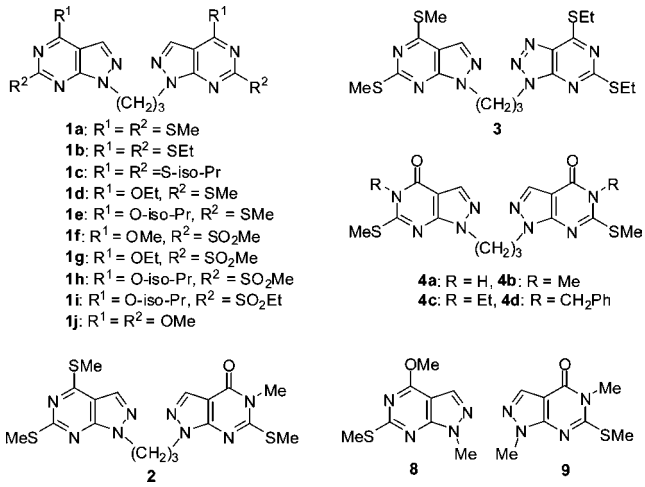


Figure 1. Pyrazolo[3,4-*d*]pyrimidine core based "propylene/Leonard linker" compounds (**1**−**4**).

Availability of so many structurally different, easily accessible preorganized compounds (**1**−**4**, Figure 1) has prompted us to make a convenient entry into pyrazolo[3,4-*d*]pyrimidinophanes, a new class of cyclophane. Normally, conformation of flexible propylene linker compounds with arene residues at their termini are open/extended, and this generalization holds even better when solid-state conformation is considered.[1h] Since in these models all four single bonds (i.e., two C−N and two C−C bonds) between two arene cores are free for unhindered rotation, they provide unbiased information about arene interaction for molecular recognition and supramolecular chemistry.

Purinophanes, which are isomeric with pyrazolo[3,4-*d*]pyrimidinophanes, were first synthesized[3] about 20 years back, and a systematic study involving synthesis and X-ray crystallography was published. Another related example involves synthesis of [3.3](3,9)carbazolophanes (*syn* and *anti*) from 1,3-dicarbazol-9-ylpropane.[4] During the past four decades, cyclophanes have been studied extensively.[5] It is generally believed that the rotation of the aromatic units is completely hindered in [2.2]cyclophanes and is more or less free for large cyclophane derivatives. Intramolecular and intermolecular CH−π and π−π interactions are observed, both in solid state and solution for [3.3]- and [4.4]cyclophanes in varying amounts.[6−13] On the basis of X-ray crystallographic structural analysis of many related propylene linker compounds (**1**−**4**, Figure 1) and many cyclophanes, propylene linker was selected as second linker for making pyrazolo[3,4-*d*]pyrimidinophanes. This choice of the propylene linker was also dictated by the fact that the angle between the least-squares planes of two pyrazolo[3,4-*d*]pyrimidinyl units in **1**−**4** varied in the range of 10.9−23.5°, thus requiring that the length of the second linker should have at least three methylene units for cyclophane formation. The corresponding values for the two most relevant compounds **4b** and **4c** are 12.4° and 10.9°, respectively.

Thus, reaction of **4a** with 1,3-dibromo propane gave four pyrazolo[3,4-*d*]pyrimidinophanes (**5-7**, ∼41%) which were separated by column chromatography on silica gel (Scheme 1).[14] Total yield in our method was significantly more than the reported yield for the synthesis of purinophanes which are isomeric with pyrazolo[3,4-*d*]pyrimidinophanes.[3] The bridge protons of these new cyclophanes show complex multiplets in their ^{1}H NMR spectra, in contrast to the first-order coupling pattern of acyclic reference compounds (**1-4**). Careful analysis of spectral data (Supporting Information) reveals formation of one symmetrical O,O- (**5** ∼9%), two dissymmetrical N,O- (**6a** and **6b** ∼27%) and one symmetrical N,N- isomer (**7** ∼5%). Out of these four products first three belong to mixed hetero/heteraphane class and last one to a heterophane subclass of cyclophanes.[5]

This product distribution looks quite surprising in view of the fact that under similar reaction conditions alkylation of **4a** with methyl iodide, ethyl iodide, or benzyl bromide gives *N*,*N*-dialkylated products **4b**, **4c**, or **4d** as major products in 88%, 45%, and 80% yields, respectively. In addition, *O*,*O*-dialkylated products are also formed in 1%, 6%, and 2% yields, respectively. The product distribution of four pyrazolo[3,4-*d*]pyrimidinophanes formed in same

(1) (a) Avasthi, K.; Chandra, T.; Bhakuni, D. S. *Indian J. Chem.* **1995**, *34B*, 944–949. (b) Biswas, G.; Chandra, T.; Avasthi, K.; Maulik, P. R. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1995**, *51*, 2453–2454. (c) Avasthi, K.; Rawat, D. S.; Maulik, P. R.; Sarkhel, S.; Broder, C. K.; Howard, J. A. K. *Tetrahedron Lett.* **2001**, *42*, 7115–7117. (d) Avasthi, K.; Farooq, S. M.; Rawat, D. S.; Sharon, A.; Maulik, P. R. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **2003**, *59*, o523–o524. (e) Avasthi, K.; Aswal, S.; Kumar, R.; Yadav, U.; Rawat, D. S.; Maulik, P. R. *J. Mol. Struct.* **2005**, *750*, 179–185. (f) Avasthi, K.; Farooq, S. M.; Aswal, S.; Raghunandan, R.; Maulik, P. R. *J. Mol. Struct.* **2007**, *827*, 88–94. (g) Avasthi, K.; Aswal, S.; Farooq, S. M.; Raghunandan, R.; Maulik, P. R. *J. Mol. Struct.* **2008**, *888*, 327–336. (h) Avasthi, K.; Farooq, S. M.; Raghunandan, R.; Maulik, P. R. *J. Mol. Struct.* **2009**, *927*, 27–36. (i) Avasthi, K.; Farooq, S. M.; Raghunandan, R.; Maulik, P. R. *J. Mol. Struct.* **2006**, *785*, 106–113. (j) Avasthi, K.; Farooq, S. M.; Bal, C.; Kumar, R.; Tewari, A. K.; Maulik, P. R. *J. Mol. Struct.* **2007**, *842*, 100–108. (k) Avasthi, K.; Rawat, D. S.; Chandra, T.; Bhakuni, D. S. *Indian J. Chem.* **1998**, *37B*, 754–759. (l) Maulik, P. R.; Avasthi, K.; Biswas, G.; Biswas, S.; Rawat, D. S.; Sarkhel, S.; Chandra, T.; Bhakuni, D. S. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1998**, *54*, 275–277. (m) Avasthi, K.; Aswal, S.; Maulik, P. R. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **2001**, *57*, 1324–1325. (n) Avasthi, K.; Tewari, A.; Rawat, D. S.; Sharon, A.; Maulik, P. R. *Acta Crystallogr. Sect.C: Cryst. Struct. Commun.* **2002**, *58*, o494−o495.

(2) Vogtle, F. *Cyclophane Chemistry: Synthesis, Structures, and Reactions*; J. Wiley: Chichester, New York, 1993.

(3) Seyama, F.; Akahori, K.; Sakata, Y.; Mitsumi, Aida, S.; M.; Nagata, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 2192–2201.

(4) Tani, K.; Tohda, Y.; Takemura, H.; Ohkita, H.; Ito, S.; Yamamoto, M. *Chem. Commun.* **2001**, 1914–1915.

(5) *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, 2004.

(6) Bogdan, N.; Condamine, E.; Toupet, L.; Ramondenc, Y.; Bogdan, E.; Grosu, I. *J. Org. Chem.* **2008**, *73*, 5831–5838.

(7) Mashraqui, S. H.; Sangvikar, Y. S.; Meetsma, A. *Tetrahedron Lett.* **2006**, *47*, 5599–5602.

(8) Ariga, K.; Toyoki, K. *Supramolecular Chemistry−Fundamentals and Applications*; Springer-Verlag: New York, 2006; p 28.

(9) Caramori, G. F.; Galembeck, S. E.; Laali, K. K. *J. Org. Chem.* **2005**, *70*, 3242–3250.

(10) Grimme, S. *Chem.−Eur. J.* **2004**, *10*, 3423–3429.

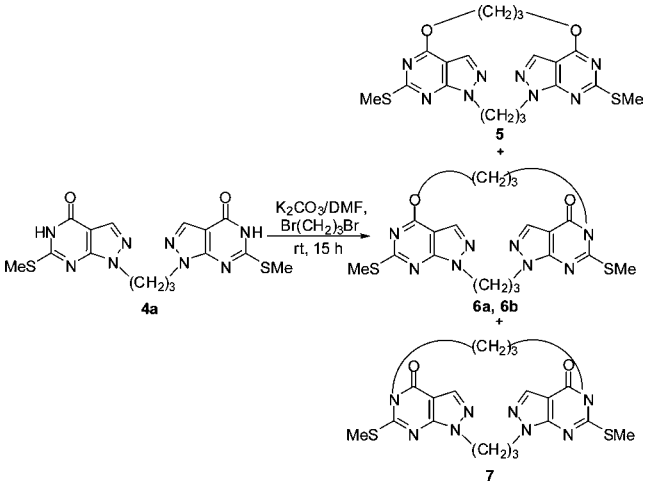
(11) Sarri, P.; Venturi, F.; Cuda, F.; Roelens, S. *J. Org. Chem.* **2004**, *69*, 3654–3661.

(12) Thilgen, G.; Azov, V. A. *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; CRC Press: New York, 2004; p 414.

(13) Kim, H. G.; Lee, C. W.; Yun, S.; Hong, B. H.; Kim, Y. O.; Kim, D.; Ihm, H.; Lee, J. W.; Lee, E. C.; Tarakeshwar, P.; Park, S. M.; Kim, K. S. *Org. Lett.* **2002**, *4*, 3971–3974.

(14) For the synthesis of **5**−**7**, see Supporting Information.

Scheme 1. Synthesis of Pyrazolo[3,4-*d*]pyrimidinophanes



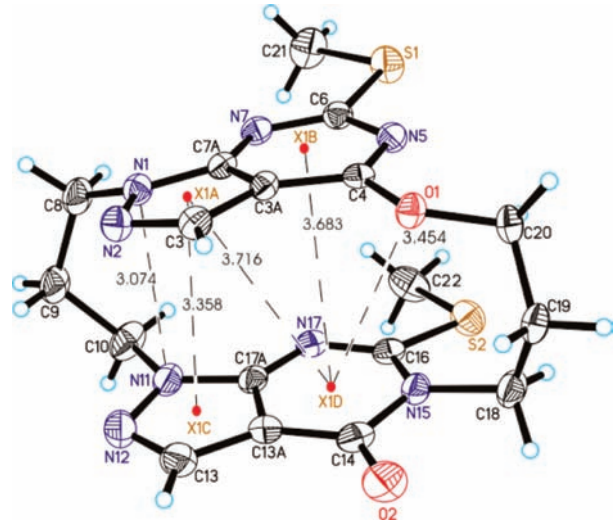


Figure 2. ORTEP diagram of **6b** (at 30% probability level) showing $\pi-\pi$ and O···Ar interactions with atomic labeling scheme

reaction clearly shows that incorporation of four atoms (−O−C−C−C−) is most favored followed by five atoms (−O−C−C−C−O−) and three atoms (−C−C−C−) in the second linker. The importance of the length of second linker for intramolecular N/O-alkylation, due to preorganization of **4a**, is strongly indicated by another experiment. Thus, reaction of **4a** with 1,2-dibromo ethane in place of 1,3-dibromo propane under identical reaction conditions gave no isolable pyrazolo[3,4-*d*]pyrimidinophanes.

Despite many attempts to grow good crystals of these new pyrazolo[3,4-*d*]pyrimidinophanes, success was achieved only with major dissymmetrical N,O-product (**6b**). The crystal structure of the first pyrazolo[3,4-*d*]pyrimidinophane (**6b**) along with numbering scheme is shown in Figure 2.[15] The solid-state structure of **6b** shows a *syn* conformation in which both pyrazolo[3,4-*d*]pyrimidinyl residues are more or less superimposed on each other. Observed conformation of **6b** resembles closely that of **1h** (normal U-motif, Figure S1, Supporting Information) and not with the other 14 compounds (**1**−**3**, Figure 1) in which pyrazolo residues are away from each other and only pyrimidinyl portions partially overlap (e.g., **1d**, unusual U-motif, Figure S2, Supporting Information). The unit cell (not shown) has four molecules of almost same conformation making two vertical pairs. One molecule from each pair is connected by C−H···N/S interactions.

Thus, an important inference from this result is that the geometry of cyclophane (**6b**) is determined mainly on the basis of length and position of two linkers connecting two arene residues by covalent bonds, whereas the conformation of related propylene linker compounds (e.g., **1**, **4b**−**4d**, etc.) is determined mainly on the basis of noncovalent arene interaction between two arene residues. The second linker required for cyclophane formation, because of its covalent nature, can easily affect the original geometry of **4a**, held mainly by weak arene interactions. For interesting comparison, other data is reported in Table S1 (Supporting Information). The angle between the least-squares planes of 9-membered pyrazolo[3,4-*d*]pyrimidinyl rings in pyrazolo[3,4-*d*]pyrimidinophane is 4.4° as compared to 12.4° and 6.7° in reference compounds **4b** and **1j**, respectively. Since there is no significant difference between 6.7° and 4.4° for **1j** and **6b**, respectively, it is quite reasonable to assume that starting material **4a** is also preorganized as a result of intramolecular arene interaction. Most noteworthy, in addition to $\pi-\pi$ interaction is the O···arene distance of 3.45 Å between the O atom of the new linker and Cg of the six-membered pyrimidine ring, indicative of strong intramolecular O···arene interaction. Very recently, a comparable distance of 3.48 Å for intramolecular O···arene interaction between the methoxy oxygen and Cg of the pentafluoro phenyl ring in another model developed for arene interactions has been reported.[16] Interestingly, weak intramolecular O···Ar interaction is also present (O···Cg = 3.681 Å) in earlier **1h**,[1g] and conformation of the new pyrazolo[3,4-*d*]pyrimidinophane (**6b**) resembles that of **1h**. None of the other propylene linker compounds (**1f**, **1g**, **1j**, or **4b**−**4d**) show any intramolecular O···arene interactions.

Because **6b** is dissymmetrical, it is of interest to know about packing arrangements from the molecular recognition angle. The two faces of **6b** can be called pyrimidine and pyrimidone for obvious reasons. One column of two vertical columns formed as a result of $\pi-\pi$, C−H−π, C−H···N, O···Ar, and S···Ar interactions and connected to the other by C−H···N and C−H···S interactions is shown in Figure 3 (left). Most important in the vertical column is the strong intermolecular O···Ar (3.24 Å) interaction approaching van der Waals contact of 3.22 Å (1.70 Å for C and 1.52 Å for O) between the O of the linker and Cg of the pyrazole ring.

(15) Crystallographic data (excluding structure factors) for **6b** has been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication CCDC No. 745431.

(16) Gung, B. W.; Zou, Y.; Xu, Z.; Amicangelo, J. C.; Irwin, D. G.; Ma, S.; Zhou, H.-C. *J. Org. Chem.* **2008**, *73*, 689–693.

It is also interesting to point out that both intra- and intermolecular O···Ar interactions involve only the O atom from the linker; the O atom from the keto group is not involved. It is interesting to mention that O···Ar interactions in water-adenine in RNA are known.[17] Lone pair aromatic interactions are of current interest, and this area has been reviewed recently.[18] Another packing picture (Figure 3, right) shows a heptamer formed as a result of weak C−H···O, C−H···N, and C−H···S interactions.

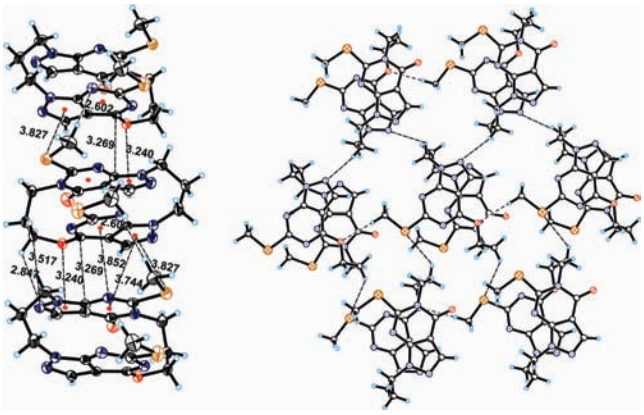


Figure 3. (Left) Part of two vertical columns formed as a result of $\pi-\pi$, C−H−π, C−H···N, and O/S···Ar interactions. (Right) Heptamer formed as a result of weak C−H···O, C−H···N, and C−H−S interactions.

Hydrogen-bonding geometry (Å, deg) for different interactions for compound **6b** are shown in Table S2 (Supporting Information). Conformation of **5**, **6a**, **6b**, and **7** in solution was assigned *anti*, *anti*, *syn*, and *anti*, respectively, on the basis of comparison of chemical shifts of SMe and the aromatic proton of the pyrazole residue with corresponding chemical shifts in monomeric 4-methoxy-1-methyl-6-methylsulfany-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8**) and 1,5-dimethyl-6-methylsulfanyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**9**) (Figure 4).

(17) Sarkhel, S.; Rich, A.; Egli, M. *J. Am. Chem. Soc.* **2003**, *125*, 8998–8999.

(18) (a) Egli, M.; Sarkhel, S. *Acc. Chem. Res.* **2007**, *40*, 197–205. (b) Alok Jain, A.; Purohit, C. S.; Verma, S.; Sankararamakrishnan, R. *J. Phys. Chem. B,* **2007**, *111*, 8680–8683.

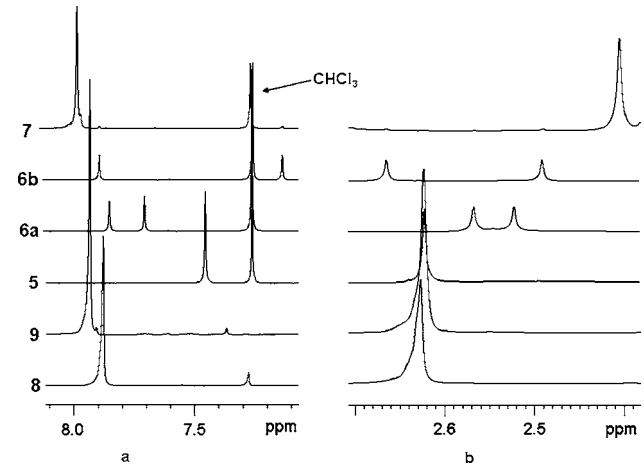


Figure 4. Stack plot of ^{1}H NMRs of **5**, **6a**, **6b**, **7**, **8**, and **9**. (a) Aromatic region; (b) SMe region

In conclusion, a very convenient entry into a new class of cyclophanes, pyrazolo[3,4-*d*]pyrimidinophanes with functionalized group (methylsulfanyl) for further chemical transformations, made from arene residues with strong propensity for intramolecular $\pi-\pi$ stacking even when connected by a single propylene linker, has been reported for the first time. The conformation of major *syn* product, **6b**, is determined by X-ray crystallography revealing the role of weak $\pi-\pi$ and O···Ar interactions for conformational control at molecular level. These compounds should prove valuable for understanding the nature of arene interactions. Work with bigger linkers with or without O/N atoms will be reported in the future.

Acknowledgment. K.A. is grateful to DST, New Delhi, India for financial support (grant no. SP/S1/G-44/99). A.A. and A.K.T. are thankful to CSIR, New Delhi, India for SRF and RA, respectively.

Supporting Information Available: Experimental details and full spectroscopic data for compounds **5**, **6a**, **6b**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902264T