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A PHOSPHINO-SUBSTITUTED ISOINDOLE OBTAINED BY CYCLIZATION OF A THIOUREA DERIVATIVE

Jorge R. Angulo-Cornejo,[b] Arancha Carbayo,[a] Elva Cueva-Talledo[a,b], José V. Cuevas,[a] Gabriel García-Herbosa,*[a] and Asunción Muñoz

[a] Area of Inorganic Chemistry. Faculty of Sciences. University of Burgos. Misael Bañuelos Square. 09001 Burgos [b] Department of Inorganic Chemistry. University National Mayor of San Marcos of Lima, Universitary City, Venezuela Avenue, Lima 100- Peru

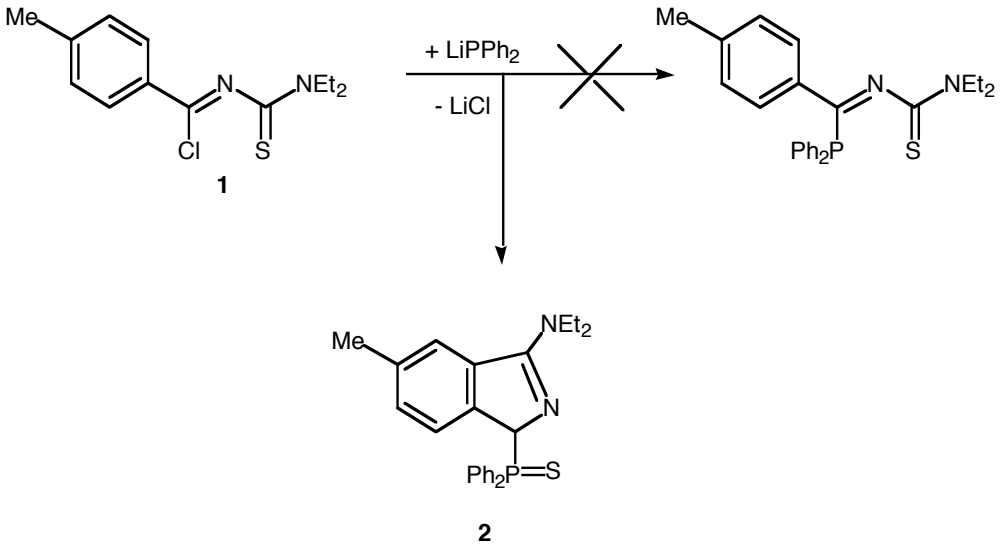
Abstract –A phosphorous functionalized isoindole derivative has been formed in the cyclization reaction of 3-chloro-*p*-tolylmethylene-1,1-diethylthiourea with lithium diphenylphosphide. The reaction involves thiourea desulfuration and C-S to P-S sulfur transfer.

INTRODUCTION

The synthesis and reactivity of organo-compounds substituted by both phosphorous and sulfur functional groups, as well as the use of chiral phosphorous and sulfur bidentate ligands in asymmetric catalysis have been recently reviewed.[1] Our interest in the synthesis of new ligands containing both P and S as donor atoms led us to explore the reaction between the thiourea derivative 3-chloro-*p*-tolyl-methylene-1,1-diethylthiourea (**1**) and lithium diphenylphosphide trying to prepare the P, S ligand 3-diphenylphosphanyl-*p*-tolylmethylene-1,1-diethylthiourea as shown in Scheme 1; however, the reaction led to a very different result. The new molecule (**2**) contains the skeleton of isoindole functionalized with a diphenylphosphinothioyl group. Several reactions leading to isoindole derivatives have been published.[2-7] Thus for instance, direct cyclization of 2-alkynylbenzonitriles,[2] as well as the palladium catalyzed version of that reaction,[3] have been reported. An acid-

* Corresponding author. Tel.: + 34 947 258822; fax: +34 947 258831; e-mail: gherbosa@ubu.es

induced cyclization of the products of vinylation of ortho palladated N, N-dimethylbenzylamines by 3-buten-2-one led to isoindolinium derivatives.[4] Dihydroisoindole-carboxylic acid esters have been prepared by using the palladium-catalyzed intramolecular α-arylation of α-amino acid esters as the key step.[5] Diverse pyridopyrroloisoindoles were prepared by palladium-catalyzed annulation of benzylidene(4-iodopyridin-3-yl)amines and aromatic substituted internal alkynes.[6] Annulation of 3-pyrrolylcarbene complexes of chromium also yielded the isoindole skeleton.[7] Thus, to the diverse published ways to synthesize molecules with the isoindole skeleton, here we report a further procedure with two additional features in the product: chirality and phosphorous functionalization.

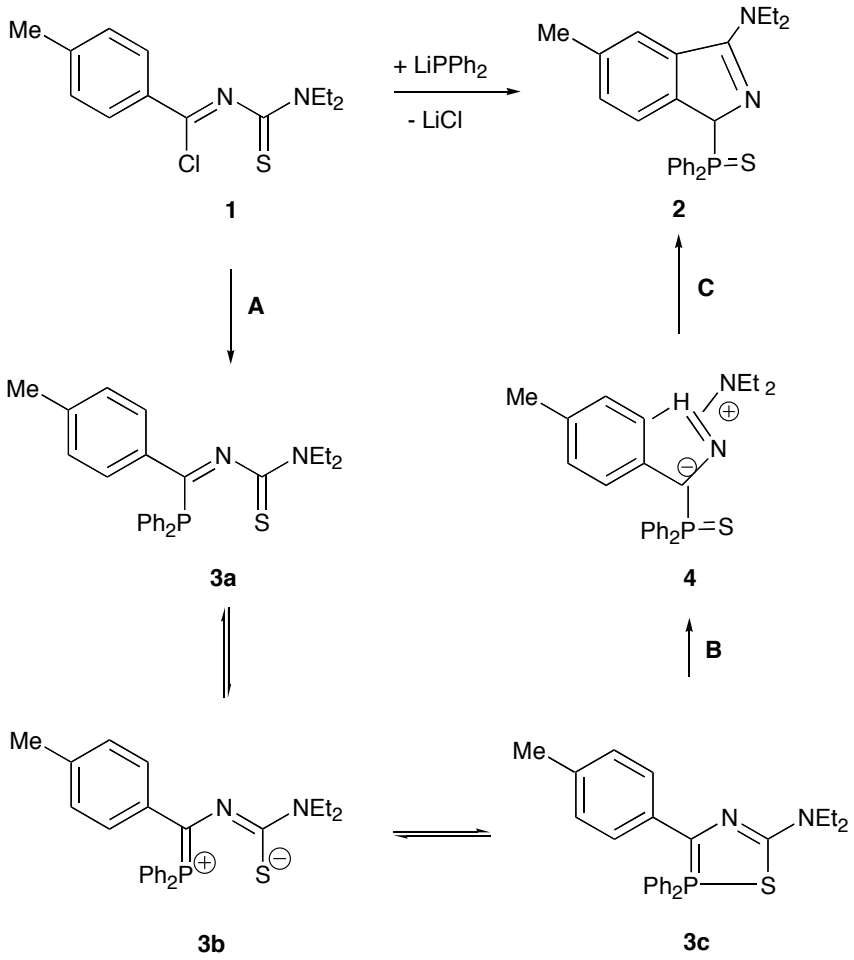


Scheme 1

RESULTS AND DISCUSSION

Treatment of 3-chloro-*p*-tolylmethylene-1,1-diethylthiourea (**1**)[8] with lithium diphenylphosphide afforded 3-(diphenylphosphinothioyl)-6-methyl-3*H*-isoindol-1-yl-diethyl-amine (**2**) in low yield. An acceptable mechanism of this cyclization reaction is proposed in Scheme 2. The formation of **2** can proceed as follows. The step A is a nucleophilic attack of the diphenylphosphido anion to the chloro-carbon bond to produce intermediate (**3**), a molecule that can be described under different resonant forms (**a**, **b** and **c**) as a derivative of [1,4,2]-thiazaphosphole containing P(V).

A related [1,3,5]-thiazaphosphole has been reported.[9] The step B involves an *E/Z* imine isomerization to intermediate (**4**). Finally, step C consists of the electrophilic attack of the carbocation to the *ortho*-carbon of the *p*-tolyl group and prototropic shift to the carbanion.



Scheme 2

The structure of **2** was determined by X-Ray crystallography (Figure 1). The molecule is chiral at C9 and, since the space group $P2_1/n$ is centric, both enantiomers *R* and *S* are present in equal numbers in the unit cell.

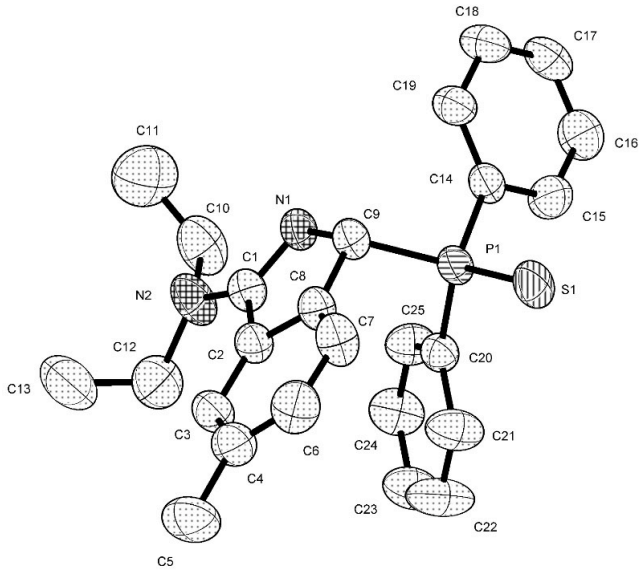


Figure 1

In order to establish whether **2** or **3** is thermodynamically more stable, DFT calculations were carried out over simplified models of the compounds at the level B3LYP/6-311G+(2d,p)//B3LYP/6-31G(d). These calculations were performed with the hybrid Beckes's three-parameter hybrid functional [10] using Lee, Yang and Parr's correlation functional [11] (B3LYP) implemented in Gaussian 03 (Revision B.04) program suite.[12] In this simplification atoms of hydrogen have replaced the phenyl groups bonded to phosphorous and the ethyl groups bonded to nitrogen. The calculations show that model for complex (**2**) is about 18 Kcal mol^{-1} more stable than the model for complex (**3**) accounting for the driving force of the steps B and C in Scheme 2.

In summary, we have found a new synthetic way to a chiral isoindole skeleton molecule from a thiourea derivative as precursor.

EXPERIMENTAL

A mixture of PPh_3 (2 g, 7.6 mmol) and finely divided lithium wire (0.142 g, 20.5 mmol) in tetrahydrofuran (20 mL) under nitrogen was stirred at rt for 2 h. The mixture was cooled at 0 ºC and NH_4Br (0.744 g, 7.6 mmol) was added. After stirring for 2 h, 3-chloro-*p*-tolylmethylene-1,1-diethylthiourea (**1**) (2.042 g, 7.6 mmol) in tetrahydrofuran (20 mL) was added dropwise. In order to remove the unreacted lithium the mixture was transferred via cannula and then refluxed by 0.5 h. The mixture was poured into a combination of water (130 mL) and dichloromethane (20 mL). The organic layer was separated, dried with Drierite® (20-40 mesh $CaSO_4$) and concentrated under reduced pressure. Successive addition of ethanol and evaporation yielded a white fine powder that was recrystallized in hexane/acetone. The colorless crystals obtained were dried under a vacuum to afford compound (**2**) (0.67 g, 21%); mp 128º C. Anal. Calcd for $C_{25}H_{27}N_2PS$: C, 71.74, H, 6.50, N, 6.69, S, 7.66. Found C, 71.73, H, 6.28, N, 6.85, S, 7.85. ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.12(6H, t, J=7.1 Hz), 2.39(3H, s), 3.52(4H, m), 5.69(1H, d, J_{P-H}=16.2 Hz), 7.10(2H, dt, J=7.8 and 3.1 Hz), 7.16(1H, d, J= 7.9), 7.25(2H, m), 7.35(2H, m), 7.54(3H, m), 7.86(1H, d, J=7.8 Hz), 8.46(2H, m). ^{13}C NMR (100 MHz,$CDCl_3$) □ 13.6, 21.7, 43.8, 71.3, 122.70, 124.81, 137.40, 137.38, 145.28, 165.39, 165.31. ^{31}P NMR (162MHz,$CDCl_3$) □ 49.20. Crystal data: $C_{25}H_{27}N_2PS$, from hexane/acetone, colorless, irregular block, ~0.6x0.6x0.3 mm, monoclinic, P2(1)/n, a = 12.6153(8) Å, b = 12.2631(8) Å, c = 14.8362(10) Å, □ = 90.9990(10)º, Vol = 2294.9 $Å^3$, Z = 4, T = 293(2) K, formula weight = 418.52, density = 1.211 g/cm^3, □ (Mo) = 0.224 mm^{-1}.

Crystallographic data (excluding structure factors) for the structure of 2 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 242125. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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REFERENCES

1. M. Gulea, S. Masson. Recent Advances in the Chemistry of Difunctionalized Organo-phosphorus and -sulfur Compounds. In *New Aspects in Phosphorus Chemistry III*, 2003, Vol. **229**, pp. 161-198.
2. M. J. Wu, L. J. Chang, L. M. Wei, and C. F. Lin. *Tetrahedron,* 1999**, 55**, 13193.
3. L. M. Wei, C. F. Lin, and M. J. Wu. *Tetrahedron Lett.,* 2000, **41**, 1215.
4. A. D. Ryabov, I. K. Sakodinskaya, S. N. Dvoryantsev, A. V. Eliseev, A. K. Yatsimirsky, L. G. Kuzmina and Y. T. Struchkov. *Tetrahedron Lett.,* 1986, **27**, 2169.
5. O. Gaertzen and S. L. Buchwald. *J. Org. Chem.,* 2002**, 67**, 465.
6. S. S. Kand, E. K. Yum, and N. D. Sung. *Heterocycles,* 2003, **60**, 2727.
7. K. H. Dotz and J. Glanzer. *Z. Naturforsch. B,* 1993, **48**, 1595.
8. U. Schroder, R. Richter, L. Beyer, J. Angulo-Cornejo, M. Lino-Pacheco, and A. Guillen. *Z. Anorg. Allg. Chem.,* 2003, **629**, 1051.
9. V. Piquet, A. Baceiredo, H. Gornitzka, F. Dahan, and G. Bertrand. *Chem. Eur. J.,* 1997, **3**, 1757.
10. A. D. Becke. *J. Chem. Phys.,* 1993, **98**, 5648.
11. C. T. Lee, W. T. Yang, and R. G. Parr. *Phys. Rev. B,* 1988, **37**, 785.
12. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople. Gaussian 03, revision B.04, Gaussian, Inc.: Pittsburgh PA, 2003.