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BIS-INDAZOLO[2,3*b*;3',2'-*f*]PYRIDAZINE: A PHOTOLABILE NEW HETEROAROMATIC SYSTEM

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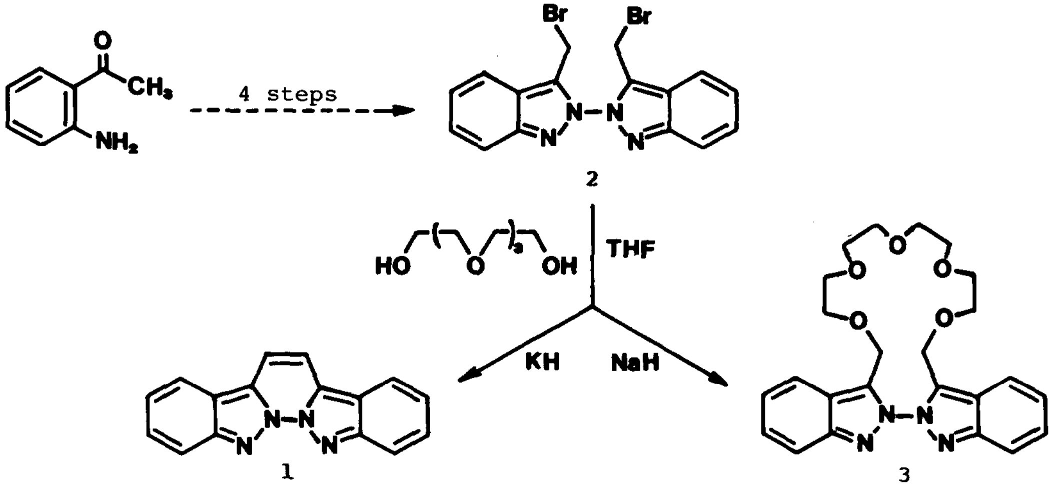
Abstract. The title compound undergoes ring opening under sunlight irradiation to give the bis-*3H*-indazole intermediate 15 which adds alcohols to give 1,2-bisindazolyl disubstituted ethanes 16a and 16b.

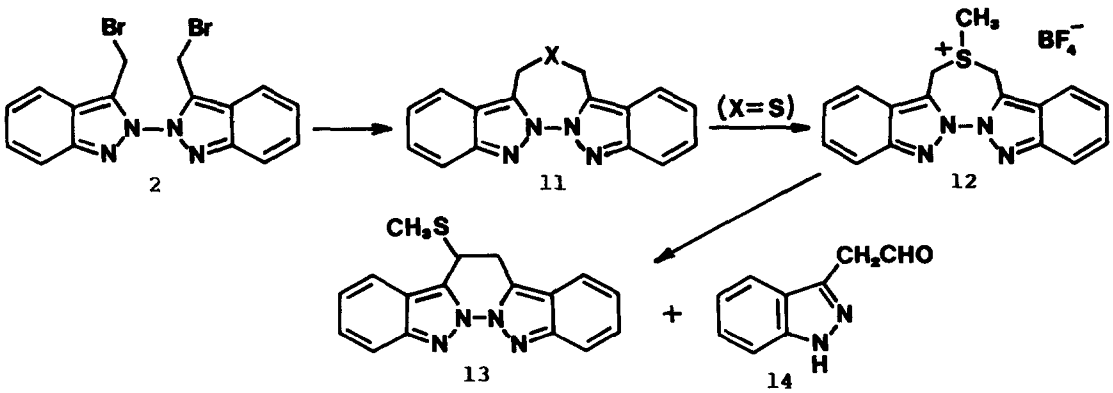
In a recent work on a new family of macrocycles incorporating 2,2'-biindazolyl subunits, we described a five-step synthesis of the crowned derivative 3 from 2-aminoacetophenone.[1] The final step was a classical cyclization reaction between the disodium salt of tetraethylene glycol and intermediate 2, affording 3 in 17% yield. Unexpectedly, when the disodium salt of tetraethylene glycol was substituted by the corresponding dipotassium salt (high dilution conditions, slow addition over 8 hours at r.t. of a solution of 2 in THF on a stirred suspension in THF of the salt, made from potassium hydride and the glycol), no macrocycle was detected in the reaction crude, but compound 1 was isolated in a 13% yield by column chromatography (silica gel, ethyl acetate) as a yellowish solid. Microanalytical and spectral data of 1 fit for a 22π-electrons structure of bis-indazolo[2,3-*b* ;3',2'-*f*]pyridazine, which is therefore the parent compound of a new heterocyclic system.[2,3]



Both NMR (chemical shifts for the central CH=CH bridge: δ8.59 for ^{1}H and δ111.1 for ^{13}C) and UV spectra (Fig. 1) account for the aromaticity of 1. In particular, the UV spectrum shows a good correspondence with those found for the related bis-pyrrolo[1,2-b;3',2'-f]pyridazine (5)[5] and 3,3'-dimethyl-2,2'-biindazole (10).[1]

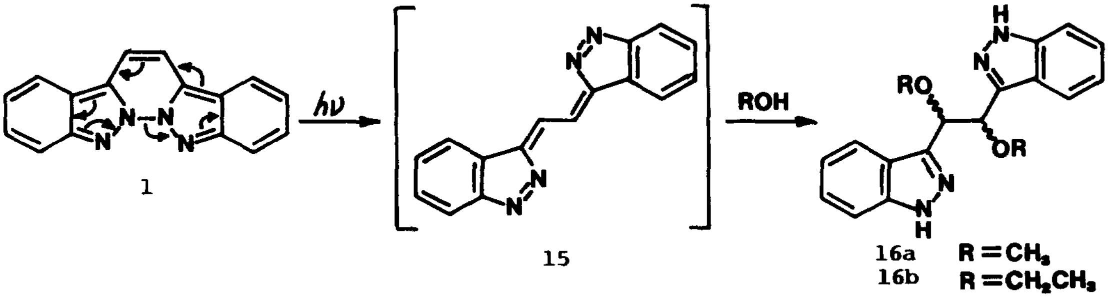
Fig. 1: UV spectra (EtOH) of 1 (———), 5[5] (·······), and 10[1] (–·–·–·).

The formation of 1 from 2 can be explained by a double HBr elimination. Surprisingly, use of other bases (K^{t}BuO, NaOEt, KH) did not gave any significant amount of 1.[7] Some attempts to prepare 1 by an alternative way were also performed. Thus, 2,2'-bis-indazolo[3,2-c;2',3'-e]dihydro(1,4,5)thiadiazepine (11, X=S) was easily obtained from 2 (slow simultaneous addition of a THF solution of 2 and an ethanolic solution of sodium sulfide over boiling ethanol, 64%).[2] Alkylation of 11 (X=S) with trimethyloxonium tetrafluoroborate afforded the unstable salt 12 (74%) which, upon base treatment (K^{t}BuO, THF), was transformed into a mixture of the expected Stevens rearrangement compound, the 1-methylthio- derivative of 1 (13)[2] (13%), and 3-(formylmethyl)indazole (14)[2] (68%), originated from 13 by a N-N' bond breaking process. However, attempts to alkylate 13 to give a sulfonium salt from which elimination to 1 could take place were unsuccessful. Alternatively, 1 could arise from SO_2 extrusion from a sulfone 11 (X=SO_2). When sulfide 11 (X=S) was oxidized with sodium periodate (MeOH, reflux), sulfoxide 11 (X=SO)[2] was obtained quantitatively. Prolonged reflux with an excess periodate resulted in decomposition of the starting material, without any formation of the sulfone 11 (X=SO_2).



The most remarkable chemical property of 1, not present in the related structures 4-7, was its photolability. Thus, a colorless dichloromethane solution of 1 was found to be stable in the dark for several days, but became intensely yellow upon exposure to sunlight. After few minutes, the new species degraded irreversibly to give again a colorless solution. Although we were unable to isolate the unstable photoproduct, the transformation was monitored by the change of the UV spectrum, showing a progressive decrease in the 292 and 365 nm bands, following first-order kinetics, with simultaneous development of a new strong absorption at 440 nm. Further sunlight irradiation caused the new band to dissapear.

To have a deeper insight on the structure of the primary photoproduct we attempted the same experiment in nucleophilic solvents. Thus, irradiation of 1 in methanol or ethanol (r.t., 6 hours) afforded the corresponding 1,2-bis-alkoxy-1,2-bis(3-indazolyl)ethane derivatives 16a and 16b, in 50% and 55% yields, respectively, as a (4:1) mixture of diastereoisomers.[2] Structures 16 allowed us to propose the structure 15 for the intermediate, which could reasonably arise from an electrocyclic opening of 1. A double addition to the electrophilic ends of 15, with simultaneous rearomatization of the indazolyl rings, would explain the ease of the addition process. Further studies on the chemical reactivity of 1 are currently underway in our laboratory.[9]

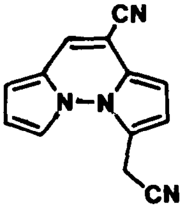


REFERENCES AND NOTES

[1] J.C. Cuevas, J. de Mendoza, and P. Prados, J. Org. Chem., 1988, 53, 2055.

[2] All new compounds gave satisfactory analyses, as well as IR and MS spectra according to their structures. Data for 1: M.p. >280°C. UV (EtOH, log ε): 235 (4.18), 292 (4.34), 303 (sh, 4.26), 315 (sh, 4.05), 365 (3.84). ^{1}H NMR (200 MHz, DMSO-d_6): 8.59 (s, 2H, CH), 8.44 (ddd, J = 8.3, 1.1, 1.0 Hz, 2H, H-4 and 4'), 8.05 (ddd, J = 8.6, 1.0, 0.9 Hz, 2H, H-7 and 7'), 7.69 (ddd, J = 8.6, 6.8, 1.1 Hz, 2H, H-6 and 6'), 7.45 (ddd, J = 8.3, 6.8, 0.9 Hz, 2H, H-5 and 5'). ^{13}C NMR (50 MHz, $CDCl_3$): 145.6 (C-7a), 127.9 (C-6), 126.7 (C-3), 122.1 (C-4), 119.1 (C-5), 116.8 (C-7), 116.0 (C-3a), 111.1 (C=C). Data for 11 (X=S): M.p. 207-208°C. ^{1}H NMR ($CDCl_3$): 7.91 (d, J = 8.8 Hz, 2H, H-7 and 7'), 7.78 (d, J = 8.5 Hz, 2H, H-4 and 4'), 7.55 (ddd, J = 8.8, 6.7, 1.1 Hz, 2H, H-6 and 6'), 7.36 (ddd, J = 8.5, 6.7, 0.9 Hz, 2H, H-5 and 5'), 4.13 (s, 4H, CH_2S). Data for 11 (X=SO): Oil. ^{1}H NMR ($CDCl_3$): 7.82 (d, J = 8.8 Hz, 2H, H-7 and 7'), 7.70 (d, J = 8.5 Hz, 2H, H-4 and 4'), 7.48 (ddd, J = 8.8, 7.7, 1.1 Hz, 2H, H-6 and 6'), 7.30 (ddd, J = 8.5, 6.7, 0.8 Hz, 2H, H-5 and 5'), 4.44-4.04 (AB system, J = 14.6 Hz, 4H, CH_2SO). Data for 12: ^{1}H NMR ($CDCl_3$): 7.92 (m, 4H, H-4, 4', 7, and 7'), 7.58 (m, 2H, H-6 and 6'), 7.42 (m, 2H, H-5 and 5'), 5.40-5.14 (AB system, J = 14.8 Hz, 4H, CH_2S), 2.99 (s, 3H, MeS). Data for 13: 7.90-7.10 (m, 8H, H-4, 4', 5, 5', 6, 6', 7, and 7'), 4.92 (m, 1H, CH), 3.80 (d, J = 4.7 Hz, 2H, CH_2), 2.06 (s, 3H, MeS). Data for 14: ^{1}H NMR ($CDCl_3$): 10.23 (s, 1H, CHO), 8.30 (d, J = 8.0 Hz, 1H, H-4), 7.50-7.33 (m, 3H, H-5, 6, and 7), 4.20 (s, 2H, CH_2). Data for 16b (4:1 mixture of diastereoisomers): M.p. 90-91°C. UV (EtOH, log ε): 210 (4.78), 255 (3.77), 290 (3.96), 300 (3.88). ^{1}H NMR ($CDCl_3$): 7.79 (d, J = 8.0 Hz, 2H, H-4 and 4'), 7.25 (m, 4H, H-6, 6', 7, and 7'), 7.00 (m, 2H, H-5 and 5'), 5.31 and 5.26 (s, 2H, CH), 3.6-3.3 (m, 4H, CH_2), 1.16 (t, J = 7.0 Hz, 6H, Me). ^{13}C NMR ($CDCl_3$): 143.7 (C-3), 140.8 (C-7a), 125.6 (C-6), 121.4 (C-3a), 120.9 (C-4), 120.5 (C-5), 110.1 (C-7), 79.6 (CH), 65.2 (CH_2), 15.3 (Me).

[3] Some heteroaromatic systems 4,[4] 5,[5] 6 and 7,[6] related to 1, with N,N'-bipyrrolyl or 4,4'-bi-1,2,4-triazolyl cores, have been reported. Chemical shift data for these 14π-electron compounds account for their aromaticity, especially when compared to the non-aromatic analogues 8[4] and 9.[5]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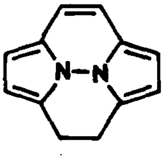
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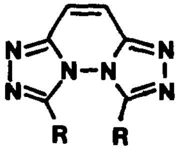
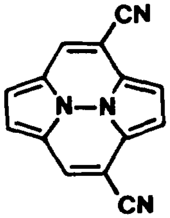

6 $R = CH_3$

7 $R = C_6H_5$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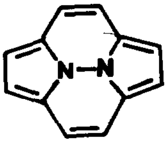
9

[4] W. Flitsch and H. Lerner, Tetrahedron Lett., 1974, 1677.

[5] W.W. Paudler and E.A. Stephan, J. Am. Chem. Soc., 1970, 92, 4468.

[6] A. Pollack and M. Tisler, Tetrahedron, 1966, 22, 2073.

[7] Reductive coupling of 2 with Ni(0), generated "in situ" from $NiCl_2(PPh_3)_2$ and Zn, was also tried. Despite the good results described in many instances for such a benzylic coupling,[8] 3-methylindazole was the only detected reaction product, due to the lability of the interconnecting N-N bond in 2.[1]

[8] M. Iyoda, M. Sakaitani, H. Otsuka, and M. Oda, Tetrahedron Lett., 1985, 26, 4777.

[9] Part of this work was presented at the 11th International Congress of Heterocyclic Chemistry, Heidelberg, Federal Republic of Germany, August 1987. Financial support from "Comisión Asesora de Investigación Científica y Técnica" (Grant 84-0410) is gratefully acknowledged.

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