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FIRST EXAMPLE OF THE SYNTHESIS OF INDOLES ON A HETEROCYCLIC MATRIX

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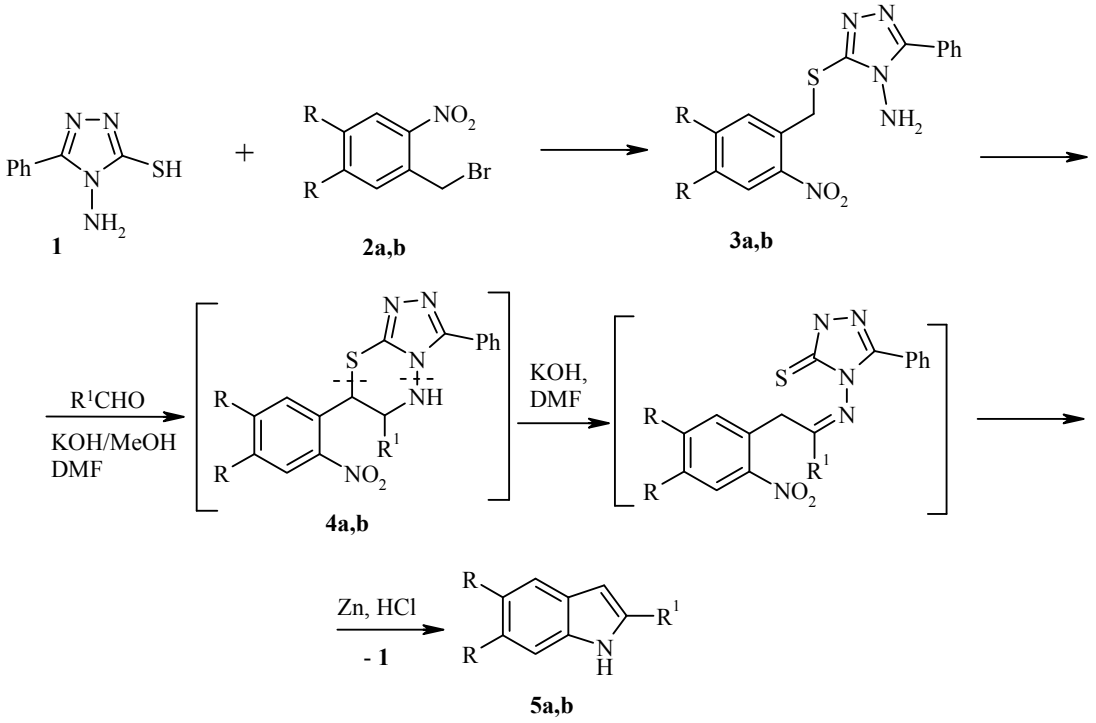
We have previously reported [1, 2] the formation of a thiadiazine derivative of type **4** from 4-amino-3-mercapto-4H-triazole **1** and its subsequent transformation with cleavage of the C–S [1] or N–N bond [2] in the presence of bases. By analyzing this type of reactivity we have proposed that the reaction involving cleavage of the C–S bond can be used in the synthesis of 2-arylindoles.



2-5 a R = H, **b** R = OMe; **4**, **5 a** R^1 = 2-furyl-5-methyl, **b** R^1 = 4-ClC_6H_4

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In fact, treatment of solutions of compounds **3a,b** (prepared by the alkylation of 4-amino-3-mercapto-triazole **1**) with the *ortho*-nitrobenzyl bromides **2a,b** [1] in DMF in the presence of the corresponding aldehydes successively with methanolic KOH solution, hydrochloric acid, and zinc gives the target indoles **5a,b**.

This method is an example of the synthesis of indoles based on a heterocyclic matrix. The 4-amino-3-mercaptotriazole **1** acts as this matrix, which can be separated from the reaction mixture.

Despite the low yields, the advantage of this route is the availability of the starting materials and simplicity of carrying out the reaction. The whole process can be realized in one pot starting with the aminotriazole **1** with successive addition of all of the components. Further study of the factors influencing the route of opening of the thiadiazine ring has allowed us to develop a novel method for the synthesis of the 2-arylindoles. These are of interest as antifungal, antimicrobial, antibacterial, and cytotoxic agents [3-7].

^{1}H NMR spectra were recorded on a Bruker DPX 250 instrument (250 MHz) using $CDCl_3$ with TMS as internal standard. Mass spectra were taken on a Kratos MS-30 spectrometer by electron impact with ionization intensity 70 eV and ionization chamber temperature 200ºC.

Synthesis of Indoles 5 (General Method). A mixture of compound **3** (50 mmol) and the corresponding aldehyde (57 mmol) in DMF (10 ml) was treated with KOH in methanol solution (5 N, 2 ml) and stirred for 3 h at room temperature. The reaction mixture on a water bath was treated dropwise with stirring with conc. HCl (4 ml) and the stirring was continued for 30 min. Zinc powder (2.9 g) was carefully added portionwise, the mixture obtained was stirred for 3 h at room temperature, and the zinc powder was removed by filtration. The filtrate was treated with KOH solution (15%, 20 ml) and then extracted with benzene (2 x 30 ml). The benzene layer was separated, concentrated, passed through a silica gel layer, evaporated to dryness *in vacuo*, and the residue was recrystallized.

2-(5-Methyl-2-furanyl)-1H-indole (5a). Yield 0.35 g (35%) as beige crystals; mp 86-87ºC (a mixture of petroleum ether and chloroform); (mp 85-86ºC [8]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 6.07 (1H, d, *J* = 3.3, H Fur); 6.50 (1H, d, *J* = 3.3, H Fur); 6.67 (1H, s, H Ind); 7.06-7.19 (2H, m, H Ar); 7.33-7.36 (1H, m, H Ar); 7.57-7.60 (1H, m, H Ar); 8.37 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 197 $[M]^+$ (100), 168 (30), 154 (60), 127 (21), 115 (10), 98 (25), 89 (53), 84 (13), 77 (20), 63 (27), 51 (29), 43 (50).

2-(4-Chlorophenyl)-5,6-dimethoxy-1H-indole (5b). Yield 0.3 g (21%) as colorless crystals; mp 210-211ºC ($CHCl_3$). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.87 (3H, s, OCH_3); 3.91 (3H, s, OCH_3); 6.67 (1H, s, H Ind); 6.84 (1H, s, H Ar); 7.04 (1H, s, H Ar); 7.34 (2H, d, AA'BB' system, *J* = 8.7, H Ar); 7.49 (2H, d, AA'BB' system, *J* = 8.7, H Ar); 8.20 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 289/287 $[M]^+$ (32/96), 274/272 (34/100), 246/244 (18/53), 227 (16), 216 (13), 210 (16), 209 (63), 201 (19), 166 (17), 161 (16), 151 (11), 144 (13), 143 (40), 91 (17), 63 (15), 59 (12), 43 (23). Found, %: C 66.92; H 5.01; N 4.78. $C_{16}H_{14}ClNO_2$. Calculated, %: C 66.79; H 4.90; N 4.87.

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REFERENCES

1. A. A. Kolodina, A. V. Lesin, and Y. V. Nelyubina, *Mendeleev Commun.*, **18**, 253 (2008).
2. A. A. Kolodina, N. I. Gaponenko, and A. V. Lesin, *Izv. Akad. Nauk, Ser. Khim.*, 1249 (2008).
3. M. Medarde, A. C. Ramos, E. Caballero, R. Peláez-Lamamié de Clairac, J. L. López, D. G. Grávalos, and A. San Feliciano, *Bioorg. Med. Chem. Lett.*, **9**, 2303 (1999).
4. G. I. Stevenson, A. L. Smith, S. G. Lewis, J. G. Neduvelil, S. Patel, R. Marwood, and J. L. Castro, *Bioorg. Med. Chem. Lett.*, **10**, 2697 (2000).

5. A. P. Kozikowski, D. Ma, J. Brewer, S. Sun, E. Costa, E. Romeo, and A. Guidotti, *J. Med. Chem.*, **36**, 2908 (1993).
6. S. Harper, B. Pacini, S. Avolio, M. Di Filippo, G. Migliaccio, R. Laufer, R. De Francesco, M. Rowley, and F. Narjes, *J. Med. Chem.*, **48**, 1314 (2005).
7. J. I. Ambrus, M. J. Kelso, J. B. Bremner, A. R. Ball, G. Casadei, and K. Lewis, *Bioorg. Med. Chem. Lett.*, **18**, 4294 (2008).
8. T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamura, and E. Shirakawa, *J. Am. Chem. Soc.*, **130**, 15823 (2008).