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SELECTIVITY IN THE THIOCYANATION OF 3-ALKYLINDOLES: AN UNEXPECTEDLY EASY ACCESS TO 2-ISOTHIOCYANO DERIVATIVES

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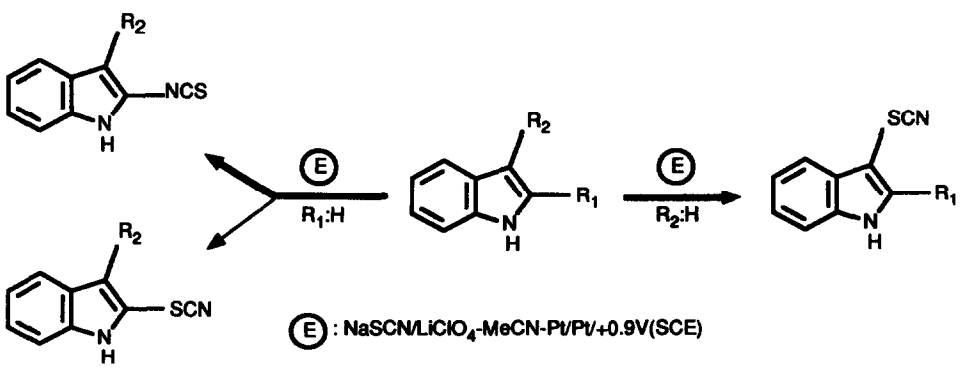
Summary. Reaction of anodically generated thiocyanogen (NaSCN, $LiClO_4$, MeCN, Pt, 0.9V *vs* SCE) with 3-alkylsubstituted indoles results preferentially in *isothiocyanation* at the indole 2-position rather than in the expected thiocyanation.

The anodic halogenation of organic compounds has been the subject of investigation for a long time and mechanistically the reaction is fairly well understood.[1] This technique is more advantageous than conventional halogenation because halogenating species can be easily generated anodically from halide ions in required amounts and no handling of hazardous or unpleasant molecules is needed.

We have already reported[2] that regioselective halogenation (chlorination, bromination,iodination) of medicinally important ergolines to the respective 2-halo derivatives can be carried out anodically at a Pt electrode in MeCN at r.t. under a constant electrode potential in the presence of $Bu_4N^+X^-$ as electro-active electrolyte. In spite of the fact that thiocyanate ion can be regarded as a pseudohalide, only a few reports seem to be available on the electrochemical thiocyanation of alkenes, dienes and aromatic compounds.[3] None of the preceding works concerned the synthetic potential of this technique towards π-excessive hetarenes (*e.g.*,indoles).[4]

We were intrigued with the anodic thiocyanation of 3-substituted indoles amongst which biologically relevant tryptophan derivatives deserve special mention. We now wish to report our preliminary results which demonstrate that *2-isothiocyano* compounds may indeed be prepared in a one-pot reaction through the electrochemical thiocyanation of 3-substituted indoles (Scheme).



The introduction of a -NCS group is currently of great interest, not only in terms of synthetic versatility, but

because of the influence of its presence on the biological activity of the substrate. In fact, this group is capable of reacting under physiological conditions with NH_2 ,imidazole, and thiol groups and it has been employed successfully in the design of a number of opioid receptor affinity labels.[5]

A general procedure is exemplified by the thiocyanation of 1*H*-indole-3-acetic acid methyl ester **1** . In the anode chamber of a three-compartment cell, equipped with Pt sheets (4x4 cm) as electrodes and SCE reference, a 0.5 M $LiClO_4$ solution in "dry" MeCN (< 0.1 M H_2O)[6](150 ml) containing **1** (1.19 g, 6.3 mmol) and NaSCN (1.125 g, 13.9 mmol) was introduced. In the cathode compartment was placed a 0.5 M $LiClO_4$ solution in "dry" MeCN (150 ml). The anolyte was blanketed with nitrogen, magnetically stirred at 20°C and electrolysed at discharge potential of SCN^-(0.9 V *vs* SCE). When 2.2 F/mol had passed, the electrolysis was interrupted and the anolyte was evaporated (< 40°C) to dryness. The crystalline residue was taken up in H_2O (200 ml) and exhaustively extracted with EtOAc (3 x 100 ml). Silica gel flash chromatography (hexane-EtOAc, 5:1) of the evaporated dried organic layer yielded sequentially 2-isothiocyanate **1N**[7](1.04 g, 67%) and 2-thiocyanate **1S**[7](108 mg, 7%). Assignment of the structures of isomeric **1N** and **1S** rested on EI-MS ($M^{+\cdot}$ *m/z* 246), IR [2060 (br,s) *vs* 2160 (sh, w) cm^{-1}] and ^1H NMR [disappearance of H-2 (d, J=2.3 Hz) at 7.11 ppm in **1**]. In addition, the assignment of structure **1S** to the more polar compound was based on the successful conversion of **1** to **1S** through two independent routes. The first involved reaction of **1** with sulphur monochloride (CH_2Cl_2,r.t.)[8] to give a mixture of dithio- and trithio-2,2'-bisindoles (**2** and **3**, respectively), followed by reduction (Zn, py-AcOH, r.t.)[9] to indolinethione **4**. Subsequent sitoselective *S*-cyanation of **4** with BrCN[10] in two-phase system (C_6H_6-H_2O) in the presence of NaOH and $Bu_4N^+HSO_4^-$ furnished thiocyanate **1S** (42 % overall yield), identical with that obtained as above. The second route involved a more efficient three-step sequence: i) oxidation (DMSO, HCl, r.t.)[11] to oxindole **5**; ii) thionation (Lawesson's reagent, toluene, rfx)[12] to **4**; iii) *S*-cyanation as above to give **1S** (51% overall). This result is of particular significance since under similar electrochemical conditions (2.4 F/mol), the 2-substituted counterpart, namely **6**, gave the 3-thiocyanoderivative **6S** in 71% isolated yield *without any trace (TLC) of the 3-isothiocyano isomer*.

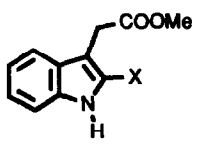
For the sake of comparison, we examined the reaction of **1** with "nascent" thiocyanogen (generated *in situ* from KSCN and Br_2 in AcOH)[13]; isothiocyanate **1N** was again the major product. The low yield of both **1N** (44%) and **1S** (9%) was probably due to the difficulty of separating the 2-bromo derivative as formed consistently well as to decomposition during work-up. An experiment carried out with $(SCN)_2$ generated according to Söderbäck [lead(II)thiocyanate, Br_2 in dry CH_2Cl_2][14] gave rise to similar poor results.

To assess the scope of the reaction, a variety of structurally different 3-substituted indoles (**7-13**) was examined. In most cases, substrates of type **N** (*e.g.*,**7-11**) were the only detected compounds (TLC) and the isolated yields of 2-isothiocyanates ranged from 41% for Boc-Val-2(NCS)Trp-OMe **10N** to 79% for **8N**.[15]

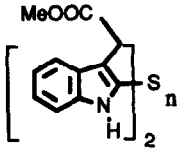
In earlier studies, Jackson *et al.* have unequivocally shown that many electrophilic substitution reactions of 3-alkyl indoles proceed by an *ipso*-attack at the 3-position , followed by rearrangement of the incoming electrophile or of the alkyl substituent already present to yield 2,3-disubstituted indoles.[16] Formation of 2-isothiocyanoindoles **N** could be explained by the unprecedented [3,5]-sigmatropic shift of the initially formed 3-thiocyano-3*H*-indolium cation **14** followed by [1,5]-hydrogen shift.[17] Accordingly, the -SCN group is well positioned to function as the *antara* component in a thermally allowed $\pi^4s+\sigma^2s+\pi^2a$, 8-electron process. The

unexceptional formation of 2-thiocyanoindoles S is considered to proceed by a direct suprafacial [1,2]-sigmatropic shift (Wagner-Meerwein rearrangement) of the thiocyano group. Although the origin of this periselectivity (3,5- *vs* 1,2-sigmatropy) is obscure, the predominating formation of 2-isothiocyanoindoles provides a practical and useful route to these compounds.

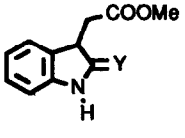
Acknowledgement. We thank the CNR (Piano finalizzato "Chimica Fine e Secondaria") for financial support.



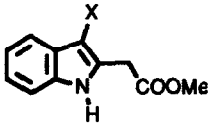
1 (X : H)
1N (X : NCS)
1S (X : SCN)



2 (n = 2)
3 (n = 3)



4 (Y : S)
5 (Y : O)



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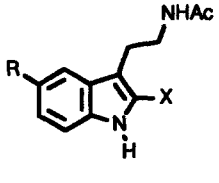
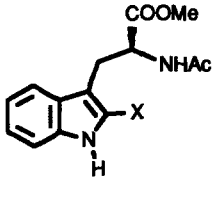


7 (R : H)
8 (R : OMe)



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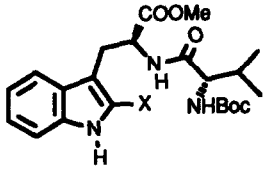

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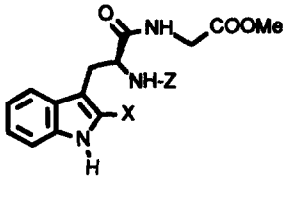

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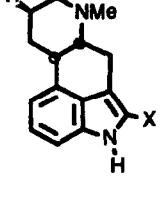
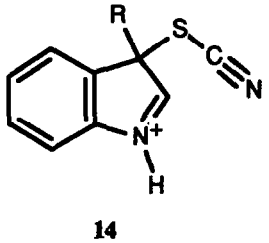


12 (R : CH_2OAc)
13 (R : COOMe)



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References and Notes

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[3] Cauquis, G., Pierre, G. *Bull.Soc.Chim.France* **1972**, 2244; *C.R.Acad.Sci.,Ser.C* **1971**, *272*, 609 [C.A. *75*, 29337z (1971)] and references cited therein. For electrochemical thiocyanation of alkenes and dienes, see Bloom, A.J., Abd Elall Eatedal, H.M., Al Ashmawy, M.I., Mellor, J.M., Owton, W.M., Abd El Samil, Z. *Stud.Org.Chem..*, **1987**, 33 [C.A. *107*, 123067n (1987)].

[4] During this investigation a thorough search of the literature, however, unearthed one example of electrochemical thiocyanation of indole itself. Misra, R.A. *Stud.Org.Chem.* **1987**, 37 [C.A. *108*, 94329 (1988)].

[5] Zimmerman, D.M., Leander, J.D. *J.Med.Chem.* **1990**, *33*, 895.

[6] The extent of oxidation products (*e.g.*, oxindole **5**) increased as the water content increased whereas the addition of a soluble base (pyridine; 2,6-lutidine; DBU) decreased or suppressed the thiocyanation reaction.

[7] Throughout this Letter, N and S designate isothiocyano and thiocyano derivatives, respectively.**1N**: R_f(hexane-EtOAc, 3:1) 0.35;λ_{max}(MeOH) 313 nm;ν_{max} ($CHCl_3$) 3460, 3215, 2060, 1735 cm^{-1};^{1}H NMR ($CDCl_3$) 8.15 (NH), 7.50 (H-4), 3.75 (CH_2 CO), 3.70 (COOMe); EI-MS *m/z* 246 (18%), 187 (40), 128 (100). **1S**: R_f 0.22; λ_{max} 278 nm;ν_{max} 3455, 3215, 2160, 1735 cm^{-1}; ^{1}H NMR 8.55 (NH), 7.64 (H-4), 7.36 (H-7), 3.90 (CH_2CO), 3.65 (COOMe); EI-MS *m/z* 246 (100%), 187 (100), 128 (41).

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[14] Söderbäck, F. *Liebigs Ann.Chem.* **1919**, *419*, 217.

[15] By standard ETh of compounds **7-13** the following compounds were isolated: **7N** (71% yield); **8N** (79%); **9N** (75%); **10N** (41%)[a]; **11N** (49%); **12N** (60%) + **12S** (17%); **13N** (58%) + **13S** (9%). [a]Undivided cell.

[16]Jackson, A.H., Lynch, P.P. *J.Chem.Soc.,Perkin Trans II* **1987**, 1483 and references quoted therein. See also, Crich, D., Davies, J.W. *Tetrahedron Lett.* **1989**, *30*, 4307. The inability of both indole-3-carbaldehyde and indole-3-nitrile to react under ETh conditions can be considered as evidence for the *ipso*-attack in the S_EAr of 3-substituted indoles.

[17] [3,5]-Sigmatropic shifts have previously been proposed as steps in rearrangement reactions, see : Battye, P.J.; Jones, D.W.; Tucker, H.P. *J.Chem.Soc., Chem.Commun.* **1988**, 495 and references cited therein.

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