Tetrahedron Vol. 42, No. 16, pp. 4511 to 4516, 1986
Printed in Great Britain.

0040-4020/86 $3.00+.00
Pergamon Journals Ltd.

SYNTHESIS OF 2-(ALKYLTHIO)INDOLES

RALF PLATE AND HARRY C.J. OTTENHEIJM*

Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED NIJMEGEN, the Netherlands

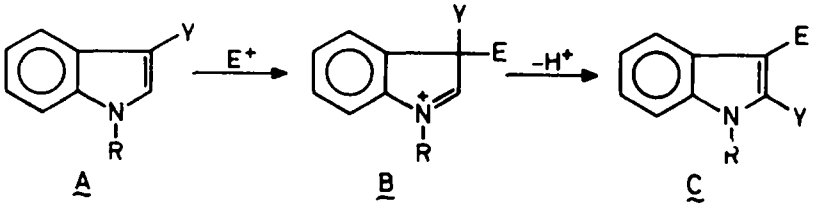
(*Received in UK* 3 *June* 1986)

Abstract - Treatment of 3-(alkylthio)indoles **3** with trifluoroacetic acid, neat (for **3a,b**) or in dichloromethane solution (for **3c,d**) at room temperature gave the corresponding 2-(alkylthio)-indoles in high yields (85-90%). The interconversion is complete and does not involve an acid-induced equilibrium between the two isomers; a mechanistic rationale is provided.

INTRODUCTION

Recently, we developed two approaches[1-3] to tryptophan derivatives having an alkylthio group at the indole C(2) position. One of these approaches[1,2] - starting from 3-(alkylthio)indoles (**A**, Y=SR) - involves a transient intermediate **B** (Y=SR, E=alkyl). We observed that the rearrangement **B**→**C** takes place when the migratory aptitude of the substituent Y is sufficient large, *i.e.* when Y is an

Scheme I



A **B** **C**

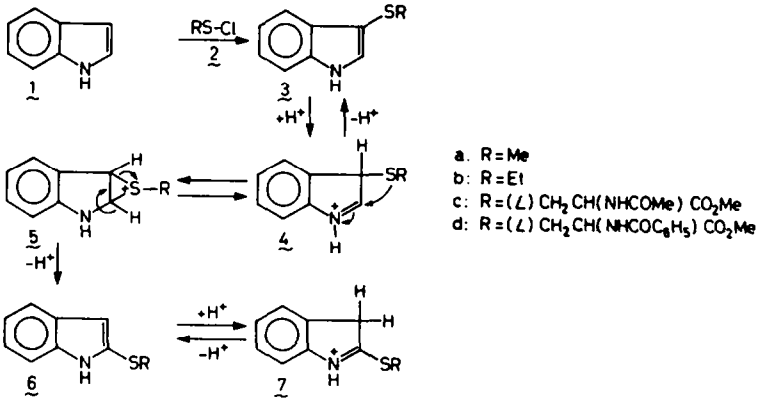
allyl- or thioalkyl group. Subsequently, we became intrigued by the relevance of Scheme I for the preparation of indoles **C** (E=H). We reasoned that if **B** (E=H) is accessible by protonation of **A**, the rearranged product **C** (E=H) might result. There is no literature report, however, on such an acid-promoted rearrangement of 3-(alkylthio)indoles[4].

Here we report that the approach outlined in Scheme I is indeed applicable for the preparation of the title compounds. The well accessible 3-(alkylthio)-indoles **A** (Y=SR) undergo an acid-catalysed rearrangement to give 2-(alkylthio)-indoles **C** (Y=SR, E=H) in high yields (86-90%). The only procedure reported so far for the synthesis of 2-(alkylthio)indoles involves the much more laborious P_2S_5 treatment of oxindoles (*i.e.* 2-hydroxyindoles) and subsequent S-alkylation[5,6].

RESULTS AND DISCUSSION

Treatment of 3a[7] or 3b[1] with CF_3COOH, either neat or as a solution in CH_2Cl_2, gave the C(2)-thioethers 6a (86%) and 6b (85%), respectively (Scheme II). Monitoring of the reaction by thin-layer chromatography showed that the conversion was complete after two hours when neat CF_3COOH was used at room temperature. The reaction took several days to reach completeness when a solution of CF_3COOH in CH_2Cl_2 was used. A mechanistic rationale for the formation of 6 is depicted in Scheme II.

Scheme II



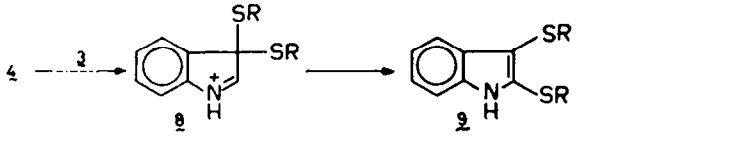
Protonation of 3 yields 4, which is in equilibrium with the sulfonium species 5. Rearomatization leads to 6. The interconversion of 3 to 6 is complete and there is no acid-induced equilibrium between these isomers. On acid treatment of *e.g.* 6a or 6c the presence of 3a or 3c could not be detected. The completeness of the interconversion can be explained as follows. Protonation of 6 yields 7, which cannot participate in the rearrangement reaction[8].

The reaction was also studied using the 3-(S-cysteinyl)indole derivatives 3c and 3d, recently prepared by us from indole (1) and the corresponding cysteinyl sulfenyl chlorides 2c and 2d, respectively[2].

Monitoring a (0.02 Molar) solution of these derivatives 3c or 3d in a mixture of CH_2Cl_2 and CF_3COOH (20/1, v/v) showed that after 35 days at room temperature the conversion to the previously unknown compounds 6c and 6d, respectively, was complete (ca 90% yield)[9].

The reactions were less clear when carried out in neat CF_3COOH; starting from 3c or 3d the rearranged products 6c and 6d were isolated, respectively, together with two other compounds in each case. In each reaction one of the side products (~15% yield) could be identified as the di-substituted indoles[2] 9c and 9d, respectively (Scheme III). The structure of the other side product is as of yet

Scheme III



unknown. The most likely explanation for the formation of 9 is provided in Scheme III. In an equilibrium mixture 4 might react with 3 to give the crossed product 8, which might rearrange to yield 9 (*cf.* 4→6). In an alternative mechanistic rationale 4 might react with 6 now to give 9 directly. Whereas we have no evidence permitting a choice between these two alternatives, the following observation might rule out the second rationale discussed. These side reactions were observed only with 3c and 3d and not with 3a and 3b. This might be explained by differences in the conversion rate 3→6. This conversion is faster for 3a and 3b, as a consequence of which these compounds are less prone to undergo the side reaction depicted in Scheme III.

Indole C(3) and C(2) thioethers are distinguishable by means of UV. Comparison of the spectra[2] of 3c and 3d and those of 6c and 6d shows for the latter compounds bathochromic shift at λ_{max} of about 9 nm. These two classes of compounds show also characteristic differences in their ^{1}H-NMR spectra. The δ-value for the C(3) proton of 2-alkylthioindoles is invariably lower (δ≤6.8 ppm)[5,6] than the δ-value for the C(2)-proton of 3-alkylthioindoles (δ≥7.0 ppm)[2,10].

In conclusion, this novel, acid-induced transposition of 3-substituted indoles has preparative significance. 2-(Alkylthio)indoles, heretofore, either unknown (4c,d) or prepared *via* several-step, low-yield sequences[5,6] (4a,b) can now be obtained in one step from readily available 3-(alkylthio)indoles. It is likely that this rearrangement will also be encountered with other indole-derivatives having a C(3)-substituent with a sufficiently high migratory aptitude. With this idea in mind it seems worthwhile to reexamine the electrophilic substitution of indoles in general. The above results add further support to our previous suggestion[1] that the formation of 2-substituted indoles might involve initial formation of a C(3)-substituted indolenine derivative followed by C(3)→C(2) migration and concomitant rearomatization.

EXPERIMENTAL SECTION

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model 555.

Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ-values (parts per million) relative to tetramethyl silane as an internal standard; deuterio chloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focussing VG 7070E spectrometer. Thin layer chromatography (TLC) was carried out by using Merck precoated silicagel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, Cl_2-TDM[11], cinnamaldehyde/HCl for indole detection[12], $AgNO_3/Na_2CrO_7$ for the detection of sulfides[13]. A miniprep LC (Jobin Yvon) has used for preparative HPLC; as stationary phase Merck silicagel H (Type 60) was used. Merck silicagel (Type 60) was used for flash chromatography.

2-(Methylthio)indole (6a)

3-(Methylthio)indole (3a)[7] (1 mmol, 163 mg) was dissolved in CF_3COOH (2 ml) and stirred at room temperature in an argon atmosphere. After 2 hours CF_3COOH was removed *in vacuo*, CH_2Cl_2 (20 ml) was added, and the solution was washed with water, dried (Na_2SO_4), filtered and evaporated to dryness *in vacuo*. Flash column chromatography and recrystallization from CH_2Cl_2/n-hexane gave 6a in 86% yield (140 mg). M.p. 47-48 °C (lit. 48-49 °C)[5]. The spectroscopical properties are identical with those reported previously[4].

2-(Ethylthio)indol (6b)

3-(Ethylthio)indole (3b)[7] (1 mmol, 177 mg) was dissolved in CF_3COOH (2 ml) and stirred at room temperature in an argon atmosphere. After 2 hours CF_3COOH was removed *in vacuo*, CH_2Cl_2 (20 ml) was added, and the solution was washed with water, dried (Na_2SO_4), filtered and evaporated to dryness *in vacuo*. Flash column chromatography gave 6b in 85% yield (150 mg), which solidified upon cooling. M.p. 36-36.5 (lit. 36-37.5 °C)[6]. The spectroscopical data are identical with those reported previously[6].

N-Acetyl-(S-indol-2-yl)-(*L*)-cysteine methyl ester (6c)

Procedure A

N-Acetyl-(S-indol-3-yl)-(*L*)-cysteine methyl ester (3c) (1 mmol, 292 mg) was dissolved in CH_2Cl_2 (50 ml) and CF_3COOH (2.5 ml) was added at room temperature. After 5 weeks of stirring in an argon atmosphere the solvents were removed *in vacuo*, and CH_2Cl_2 was added. The solution was washed with water, dried (Na_2SO_4), filtered and evaporated. The residue was submitted to flash column chromatography to yield 6c as a foam (90%, 263 mg) which was homogeneous on tlc; R_f 0.50 (MeOH, CH_2Cl_2, 5/95, v/v). UV (MeOH) λ_{max}=295 (sh), 287, 280 (sh), 225 nm; λ_{min}=251 nm. EIMS (70 eV) m/e=292 $[M]^+$, 39%), 150 (46%), 149 ($[C_8H_7NS]^+$, 40%), 144 ($[C_6H_{10}NO_3]^+$, 100%); exact mass calcd. for $C_{14}H_{16}N_2O_3S$ 292.0882, found 292.0880. ^1H NMR (90 MHz, $CDCl_3$) δ=9.60 (s(br), 1H, indole NH), 7.60-6.80 (m, 4H, indole C(4)-C(7)H), 6.75 (d, ^4J=1 Hz, 1H, indole C(3)H), 6.20 (d(br), 1H, NHCO), 4.90 (X part of ABX spectrum, $^3J_{AX}$=4 Hz, $^3J_{BX}$=8.5 Hz, 1H, SCH_2CH), 3.67 (s, 3H, OCH_3), 3.25 and 2.95 (AB part of ABX spectrum, $^3J_{AX}$=4 Hz, $^3J_{BX}$=8.5 Hz, $^2J_{AB}$=14 Hz, 2H, SCH_2CH), 2.07 (s, 3H, $COCH_3$).

Procedure B

N-Acetyl-(S-indol-3-yl)-(*L*)-cysteine methyl ester (3c) (1 mmol, 292 mg) was dissolved in CF_3COOH (2 ml) and stirred at room temperature for 16 hrs in an argon atmosphere. Work-up as described above and HPL chromatography (silicagel 60H; MeOH/CH_2Cl_2, 2/98, v/v) gave 6c as a foam in 45% yield (130 mg) and 9c[2] (15%, 60 mg).

Compound 9c: m.p. 146-148 °C (EtOH/n-hexane). R_f 0.25 (MeOH, CH_2Cl_2, 5/95, v/v). UV (MeOH) λ_{max}=300 (sh), 292, 210 nm; λ_{min}=260 nm. EIMS (70 eV) m/e=467 ($[M]^+$, 17%), 324 ($[M-C_6H_9NO_3]^+$, 8%), 181 ($[M-2\times C_6H_9NO_3]^+$, 9%); 144 ($[C_6H_{10}NO_3]^+$, 100%); exact mass calcd. for $C_{20}H_{25}N_3O_6S_2$ 467.1185, found 467.1183. ^1H-NMR (90

MHz, $CDCl_3$) δ=10.40 (s(br), 1H, indole NH), 7.80-7.10 (m, 4H, indole C(4)-C(7)H), 6.80 (d(br), 1H, NHCO), 6.65 (d(br), 1H NHCO), 4.95-4.65 (2 X part of ABX spectrum, 2H, 2×SCH_2CH), 4.00-2.90 (2 AB part of ABX spectrum, 4H, 2×SCH_2CH), 3.65 and 3.20 (2×s, 6H, 2×OCH_3), 2.10 and 1.85 (2×s, 6H, 2×$NHCOCH_3$). Anal. calcd. for $C_{20}H_{25}N_3O_6S_2$ (M=467.563) C 51.38, H 5.39, N 8.99, found C 51.56, H 5.39, N 8.97.

N-Benzoyl-(S-indol-2-yl)-(*L*)-cysteinyl methyl ester (6d)

Procedure A

Compound 6d was obtained from 3d (1 mmol, 354 mg) in 87% yield (310 mg) according to procedure A described above for the synthesis of 6c. R_f 0.50 (MeOH, CH_2Cl_2, 2/98, v/v). M.p. 129-130 °C. UV (MeOH) λ_{max}=295 (sh), 288, 280 (sh), 215 nm; λ_{min}=251 nm. EIMS (70 eV) m/e=354 $[M]^+$, 27%), 206 ($[M-C_8H_7NS]^+$, 70%), 149 ($[C_8H_7NS]^+$, 23%), 148 ($[C_8H_7NS]^+$, 21%), 105 ($[C_7H_5O]^+$, 100%); exact mass calcd. for $C_{19}H_{18}N_2O_3S$ 354.1038, found 354.1048. ^1H NMR (60 MHz, $CDCl_3$) δ=9.5 (s(br), 1H, indole NH), 7.7-7.0 (m, 10H, indole C(4)-C(7)H, C_6H_5 and NHCO), 6.75 (d, ^4J=1 Hz, 1H, indole C(3)H), 5.1 (X part of ABX spectrum, $^3J_{AX}$=8 Hz, $^3J_{BX}$=4 Hz, 1H, SCH_2CH), 3.65 (s, 3H, OCH_3), 3.45 and 2.95 (AB part of ABX spectrum, $^3J_{AX}$=8 Hz, $^3J_{BX}$=4 Hz, $^2J_{AB}$=14 Hz, 2H, SCH_2CH).

Procedure B

N-Benzoyl-(S)-indol-3-yl)-(*L*)-cysteine methyl ester (3d) (1 mmol, 354 mg) was dissolved in CF_3COOH (2 ml) and stirred for 16 h in an argon at room temperature. Work-up as described above and HPL chromatography (silicagel 60H; MeOH/CH_2Cl_2, 1/99, v/v) gave 6d as a foam in 48% yield (170 mg) and 9d[2] (13%, 75 mg).

Compound 9d[2]: m.p. 176-177 °C (methanol/ethyl acetate). UV (MeOH) λ_{max}=300 (sh), 290, 230 nm; λ_{min}=262 nm. EIMS (70 eV) m/e=591 $[M]^+$, 2%), 386 ($[M-C_{11}H_{11}NO_3]^+$, 8%), 206 ($[C_{11}H_{12}NO_3]^+$, 18%), 181 ($[M-2\times C_{11}H_{11}NO_3]^+$, 3%); 105 ($[C_6H_5O]^+$, 100%); exact mass calcd. for $C_{38}H_{29}O_6S_2$ 591.1498, found 591.1476. ^1H-NMR (90 MHz, $CDCl_3$) δ=10.50 (s(br), 1H, indole NH), 7.90-7.00 (m, 16H, indole C(4)-C(7)H), 2×C_6H_5, 2×CONH), 5.20-4.80 (2 X part of ABX spectrum, 2H, 2×S-CH_2CH), 3.80 and 2.90 (2 AB part of ABX spectrum, 4H, 2×S-$CHCH_3$), 3.65 and 3.25 (2×s, 6H, 2×OCH_3). Anal. calcd. for $C_{38}H_{29}N_3O_6S_2$ (M=591.705) C 60.65, H 4.93, N 7.04, found C 60.65, H 4.93, N 7.04.

REFERENCES

1. Plate, R.; Ottenheijm, H.C.J.; Nivard, R.J.F. *J. Org. Chem.* 1984, *49*, 540.
2. Plate, R.; Nivard, R.J.F.; Ottenheijm, H.C.J. *Tetrahedron* 1986, accompanying communication.
3. Plate, R.; Theunisse, A.W.G.; Ottenheijm, H.C.J. manuscript submitted.
4. This is surprising as the corresponding reaction involving alkyl substituents (B, Y=E=Alkyl) has been well-studied, see *e.g.* Jackson, A.H.; Smith, P. *Tetrahedron* 1968, *24*, 2227.
5. Hino, T.; Tsuneoka, K.; Nakagawa, M.; Akaboshi, S. *Chem. Pharm. Bull.* 1969, *17*, 550.
6. Nakagawa, M.; Hino, T. *Tetrahedron* 1970, *26*, 4491; Hino, T.; Nakagawa, M., Akaboshi, S.: *J. Chem. Soc. Chem. Commun.* 1967, 657.
7. Tomita, K.; Terada, A.; Tachikura, R. *Heterocycles* 1976, *4*, 729.

8. This finding is in contrast to the chemistry of pyrrolyl sulfides which have been demonstrated to exist in acid-mediated equilibrium. De Sales, J.; Greenhouse, R.; Muchowski, J.M. *J. Org. Chem.* 1982, *47*, 3668.
9. Recent interest in S-aryl cysteine derivatives has been demonstrated. Hickman, R.J.S.; Christie, B.J.; Guy, R.W.; White, T.J. *Aust. J. Chem.* 1985, *38*, 899.; Flynn, G.A.; Beight, D.W. *Tetrahedron Lett.* 1984, *25*, 2655.
10. Jardin, R.V.; Brown, R.K. *Can. J. Chem.* 1965, *43*, 1298.
11. Arx, E. von; Faupel, M.; Bruggen, M. *J. Chromatogr.* 1976, *120*, 224.
12. Anfaerbereagentien fuer Duennschicht- und Papierchromatographie, Fa. Merck, Darmstadt, F.R.G., 1970, 108.
13. Knight, R.H.; Young, L. *Biochem. J.* 1958, *70*, 111.