SYNTHESIS OF 2-METHYLTHIO-3*H*-INDOL-3-ONE 3-OXIMES FROM 1-(-*N*-ARYLAMINO)-1-METHYLTHIO-2-NITROETHENES

Timothy Kearney and John A. Joule*
Department of Chemistry, University of Manchester,
Manchester M13 9PL, U. K.
Arthur Jackson
Fine Organics Ltd., Seal Sands, Middlesbrough,
Cleveland TS2 1UB, U. K.

Abstract - 1-(*N*-Arylamino)-1-methylthio-2-nitroethenes, prepared by reaction of the arylamine with 1,1-bis(methylthio)-2-nitroethene, are converted into 2-methylthio-3*H*-indol-3-one 3-oximes by treatment with triflic acid at room temperature.

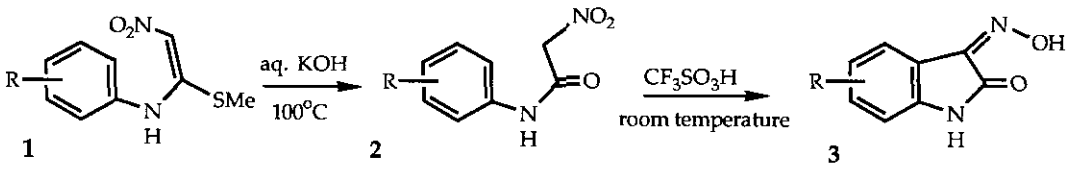
Relatively few methods exist for the synthesis of indolones[1] (3*H*-indol-3-ones): in the Bayer synthesis[2] (for 2-arylindolones) a 2-arylindole is 3-nitrosated, reduced to 3-amine, oxidised to indolone-imine and this then hydrolysed. Hot phosphorus pentachloride converts isatin into 2-chloroindolone and this electrophilic species can be made to react with electron-rich aromatics affording 2-aryl-substituted indolones,[3] and with amines affording 2-aminoindolones.[4]

Isatins[5] (1*H*-indole-2,3-diones) are useful intermediates, for example in the synthesis of indolo[2,3-*b*]quinoxalines,[6] oxindoles,[7] *o*-aminobenzonitriles,[8] (*via* isatin oximes), the Pfitzinger modification of the Friedländer synthesis to produce 4-carboxyquinolines,[9] indole-2,3-dicarboxylic acids,[10] and various indole-related biologically active substances.[11] Indeed, isatin itself has been shown to be the biologically active chemical produced by an *Alteromonas* sp. strain inhabiting the surface of embryos of the caridean shrimp *Palaemon macrodectylus*, which protects them from the otherwise lethal effects of infection by the pathogenic fungus *Lagenidium callinectes*.[12]

The most frequently used ring-synthetic route to isatins is that of Sandmeyer[5,13] in which an aniline is reacted with chloral hydrate and hydroxylamine to generate an anilide of glyoxylic acid oxime, which is then subsequently ring-closed using strong acid. There have been reports that hydrogen cyanide can be a byproduct in such ring closures.[14]

An early preliminary report,[15] that 2-nitro-*N*-phenylacetamide could be converted into isatin 3-oxime using concentrated sulphuric acid at 30°C or anhydrous hydrogen fluoride at 75°C, was

recently re-examined and shown to be the prototype of a general process (Scheme 1), the preferred acid for the room temperature conversion of 2-nitro-*N*-arylacetamides (**2**) into isatin 3-oximes (**3**) being shown to be trifluoromethanesulphonic (triflic) acid.[16] It was also shown that isatin 3-oximes can be hydrolysed by warm concentrated hydrochloric acid acid to afford isatins.



Scheme 1

Since the 2-nitro-*N*-arylacetamides utilised were in turn prepared from 1-(*N*-arylamino)-1-methylthio-2-nitroethenes (**1**) by alkaline hydrolysis, it seemed not unreasonable that the latter, themselves might suffer a ring closure, under appropriate acidic conditions, to give bicyclic products containing an indole nucleus, at the same oxidation level as an isatin.

We have now examined the reaction of a range of 1-(*N*-arylamino)-1-methylthio-2-nitroethenes (**1**) with strong acid. Concentrated sulphuric acid treatment led to no useful products however the use of triflic acid, at room temperature, led in all cases to the formation of orange-red bicyclic

Table 1

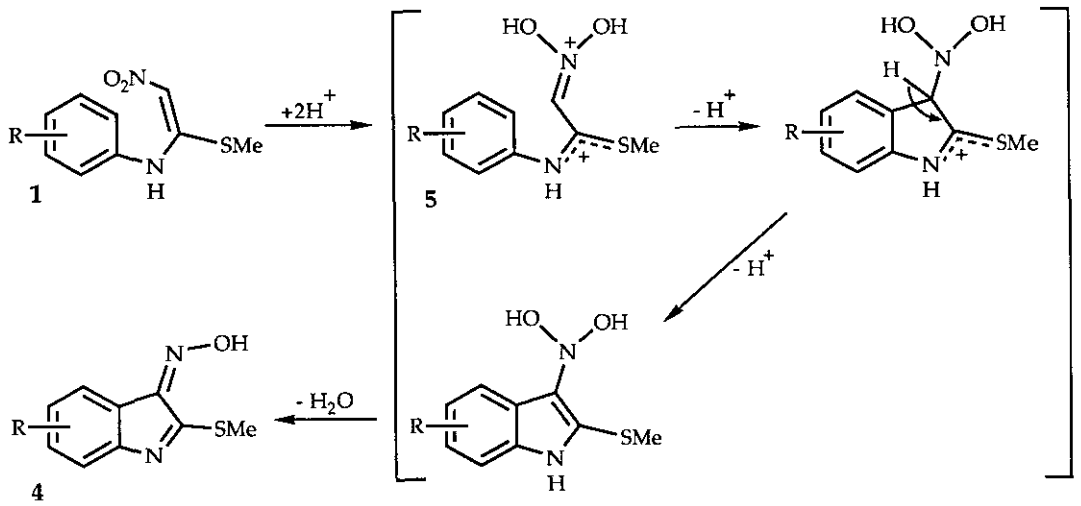
2-Methylthio-3*H*-indol-3-one 3-oximes (**4**) prepared using triflic acid at room temperature.

Product	R	Yield (%)[a]	Reaction time (h)	mp (°C)[b]	Molecular Formula
4a	H	17	16	183-185	$C_9H_8N_2OS$
4b	5-Me	30	12	203-205	$C_{10}H_{10}N_2OS$
4c	6-Me	20	12	113-115	$C_{10}H_{10}N_2OS$
4d	7-Me	22	12	175-177	$C_{10}H_{10}N_2OS$
4e	5-F	18	36	178-180	$C_9H_7FN_2OS$
4f	6-F	14	35	203-205	$C_9H_7FN_2OS$
4g	7-F	15	36	175-177	$C_9H_7FN_2OS$
4h	5-Cl	30	24	224-226	$C_9H_7ClN_2OS$
4i	6-Cl	27	24	207-208	$C_9H_7ClN_2OS$
4j	7-Cl	25	24	225-227	$C_9H_7ClN_2OS$
4k	6-Br	29	24	200-202	$C_9H_7BrN_2OS$
4l	5-OMe	15	1	210-211	$C_{10}H_{10}N_2O_2S$
4m	6-OMe	12	1	208-209	$C_{10}H_{10}N_2O_2S$

a Yields are of column-purified materials

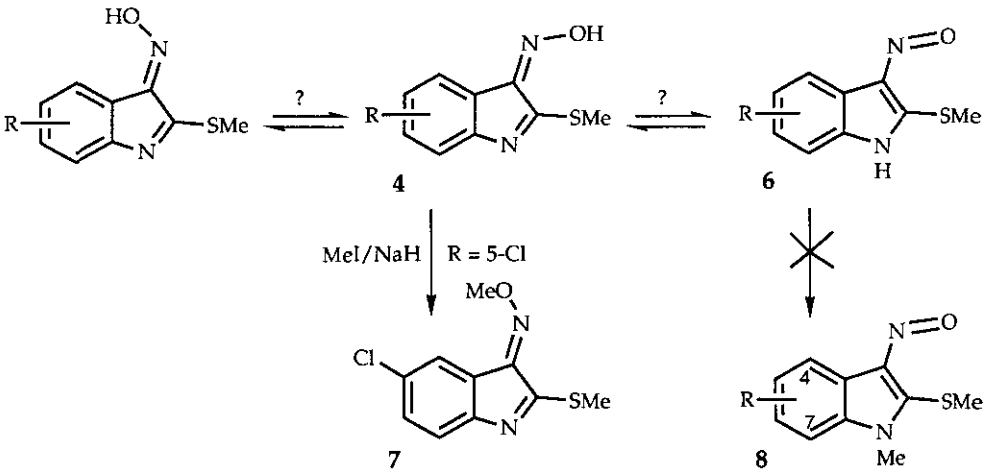
b Melting points are of column-eluate-evaporated materials

products (Tables 1 and 2) which were shown to have the constitution of 2-methylthio-3*H*-indol-3-one 3-oximes (**4**). One may view the process (Scheme 2) as being initiated by nitro-group double protonation[17] generating a species (**5**) in which cyclising electrophilic attack on the aromatic ring, followed by loss of water produces the observed products (**4**).



Scheme 2

In principle, the methylthioindolones (**4**) could exist as tautomeric nitroso-indoles (**6**). 5-Chloro-2-methylthio-3*H*-indol-3-one 3-oxime was reacted with methyl iodide in the presence of sodium hydride to afford a monomethyl derivative, which on the basis of the chemical shift of the introduced methyl group, δ 4.25, is the *O*-methyl-derivative (**7**) but since no close models exist for the chemical shift of a methyl in the alternative situation (**8**) further confirmation for this



assignment was sought. An nOe experiment provided this evidence: the *O*-methyl and the 4-hydrogen were shown to be close (15%), but there was no nOe observed between the introduced methyl and the ring H-7, such as would have been expected for the *N*-methylated isomer (**8**). The nOe experiment also proves that, at least in the methylated product, the geometry of the oxime C:N is *E*, as shown in **7**. The UV/VIS absorption spectra of 5-chloro-indolone (**4h**), and its *O*-methylated derivative, recorded in ethanol were very similar, from which we conclude that for (**4h**), the oxime tautomer does indeed represent the predominant species. Further, since all products (**4**) had closely comparable UV/VIS absorptions (Table 2) we believe that all exist predominantly as oxime tautomers in solution.

Alkaline hydrolysis of **4e** and **4h** afforded 5-fluoro- and 5-chloroisatins in high yields, showing that this route provides an alternative means for the synthesis of isatins.

EXPERIMENTAL

2-Methylthio-3*H*-indol-3-one 3-Oximes (4); General Procedure

The 1-(*N*-arylamino)-1-methylthio-2-nitroethene (**1**)[16] (1 g, *ca*. 4.5 mmol), was dissolved cautiously in trifluoromethanesulphonic acid (10 ml, 67 mmol) at 0°C, the solution was allowed to come to room temperature, and maintained at that temperature until tlc analysis indicated that all starting material had been consumed. The solution was quenched by addition to ice-water and product was isolated by extraction into ether. The 2-methylthioindolone oxime (**4**) was purified by chromatography over silica eluting with $CHCl_3$/EtOH (95:5).

Methylation of 5-chloro-2-methylthio-3*H*-indol-3-one 3-oxime

The methylthio-oxime (**4h**) (50 mg, 0.26 mmol), methyl iodide (31 mg, 0.22 mmol) and sodium hydride (6 mg, 0.25 mmol) were stirred together in DMF (1.5 ml) at room temperature for 12 h. The mixture was quenched with ice-cold aqueous 5% ammonium chloride and organic product was extracted into chloroform. Chromatography of crude material, obtained by evaporation, over silica eluting with $CHCl_3$/EtOH (9:1) yielded the *O*-methyl product (**7**) (34 mg, 64%), mp 106-107°C (from EtOH), $\lambda_{max.}$ (EtOH) 267, 321sh, and 426 nm (log ε 4.69, 3.81, and 3.59); δ_H ($CDCl_3$) 2.65 (3H, s, SCH_3), 4.25 (3H, s, OCH_3), 7.20 (1H, d, J 8Hz, H-7), 7.30 (1H, dd, J 2, 8 Hz, H-6), 7.85 (1H, d, J 2 Hz, H-4); $\nu_{max.}$ (nujol) 1657 cm^{-1}; *m/z* (EI) 240 (45, M^+), 209 (100), 194 (62), 182 (12). Anal.Calcd for $C_{10}H_9N_2OClS$: C, 50.0; H, 3.8; N, 11.7; Cl, 14.8; S, 13.3. Found: C, 49.9; H, 3.8; Cl, 14.9; N, 11.7; S, 13.3.

Hydrolysis of 5-fluoro- and 5-chloro-2-methylthio-3*H*-indol-3-one 3-oximes

The methylthioindolone oxime (**4e** and **4h**) (100 mg, *ca*. 0.5 mmol) was heated at reflux in aqueous potassium hydroxide (0.1N, 10 ml, 1 mmol) for 8 h, and slowly dissolved. The cooled

Table 2

Spectroscopic and Analytical data for 2-methylthio-3*H*-indol-3-one 3-oximes (**4**).

Product	Found (%) or (M^+)	Required (%) or (M)	$\lambda_{max.}$ (log ε) (EtOH)	δ_H (J in Hz)	E I ms *m/z* [a] (%)
4a	C, 56.0; H, 4.0; N, 14.2; S, 16.2	C, 56.3; H, 4.2, 14.6; S, 16.7	261 (4.43), 323 (4.28), 404 (3.32)	(CD_3OD) 2.65 (3H, s), 7.28 (1H, t, J 8), 7.40 (1H, d, J 8), 7.50 (1H, t, J 8), 8.10 (1H, d, J 8)	192 (11), 175 (33), 160 (16), 43 (100)
4b	C, 57.9; H, 5.0; N, 13.2; S, 15.2	C, 58.3; H, 4.9; N, 13.6; S, 15.5	264 (4.37), 321 (3.26), 418 (3.03)	(($CD_3)_2O$) 2.35 (3H, s), 2.60 (3H, s), 7.18 (1H, d, J 8), 7.22 (1H, d, J 8), 7.88 (1H, s)	206 (64), 189 (100), 174 (49), 143 (25)
4c	C, 58.0; H, 4.8; N, 13.4; S, 15.4	C, 58.3; H, 4.9; N, 13.6; S, 15.5	264 (4.19), 328 (3.32), 396 (2.98)	(CD_3OD) 2.35 (3H, s), 2.60 (3H, s), 7.10 (1H, dd, J 3, 8), 7.21 (1H, d, J 3), 7.95 (1H, d, J 8)	206 (23), 192 (42), 175 (54), 160 (28), 45 (100)
4d	C, 57.8; H, 4.6; N, 13.3; S, 15.2	C, 58.3; H, 4.9; N, 13.6; S, 15.5	261 (4.55), 330 (3.57), 411 (3.43)	(($CD_3)_2O$) 2.40 (3H, s), 2.60 (3H, s), 7.06 (1H, t, J 8), 7.23 (1H, dd, J 2, 8), 7.84 (1H, dd, J 2, 8)	206 (64), 189 (100), 174 (27), 142 (27)
4e	C, 51.3; H, 3.6; N, 12.6; F, 8.4; S,15.1	C, 51.4; H, 3.3; N, 13.3, F, 9.0; S,15.2	264 (4.56), 325 (3.58), 412 (3.34)	(($CD_3)_2O$) 2.60 (3H, s), 7.18 (1H, m), 7.31 (1H, dd, J 4, 8), 7.73 (1H, DD, J 3, 8)	210 (33), 193 (44), 178 (41), 147 (40), 137 (40), 43 (100)
4f	C, 51.2; H, 3.6; N, 12.8; F, 8.5; S,15.1	C, 51.4; H, 3.3; N, 13.3, F, 9.0; S,15.2	265 (4.36), 322 (3.66), 410 (3.40)	(($CD_3)_2SO$) 2.6 (3H, s), 6.85 (1H, m), 7.05 (1H, dd, J 3, 9), 8.02 (1H, dd, J 6, 9)	210 (29), 193 (43), 178 (32), 166 (5), 147 (15), 40 (100)
4g	C, 51.2; H, 3.5; N, 12.7; F, 8.4; S,15.0	C, 51.4; H, 3.3; N, 13.3, F, 9.0; S,15.2	266 (4.42), 326 (3.60), 406 (3.20)	(($CD_3)_2O$) 2.60 (3H, s), 7.20 (2H, m), 7.85 (1H, m)	210 (61), 193 (100), 178 (89), 166 (11), 147 (15)
4h	C, 48.2; H, 3.1; N, 11.9; Cl,15.6; S,13.7	C, 47.7; H, 3.1; N, 12.4; Cl,15.7; S,14.1	267 (4.64), 320sh (3.67), 417 (3.52)	(($CD_3)_2SO$) 2.65 (3H, s), 7.45 (1H, d, J 8), 7.55 (1H, dd, J 2, 8), 14.0 (1H, br s)	226 (54), 209 (100), 194 (96), 178 (38), 163 (39)
4i	C, 47.4; H, 2.8; N, 11.9; Cl,15.5; S,13.7	C, 47.7; H, 3.1; N, 12.4; Cl,15.7; S,14.1	269 (4.55), 328 (3.58), 400 (3.19)	(($CD_3)_2SO$) 2.60 (3H, s), 7.20 (1H, d, J 8), 7.32 (1H, s), 7.90 (1H, d, J 8)	226 (56), 209 (100), 194 (50)
4j	C, 47.5; H, 2.9;N, 12.0; Cl,15.4; S,13.6	C, 47.7; H, 3.1; N, 12.4; Cl,15.7; S,14.1	268 (4.31), 329 (3.60), 410 (3.25)	(CD_3OD) 2.65 (3H, s), 7.20 (1H, t, J 8), 7.50 (1H, d, J 8), 8.20 (1H, d, J 8)	226 (77), 209 (100), 194 (57)
4k	M, 269.9457	M, 269.9463	270 (4.62), 329 (3.76), 385 (3.39)	(($CD_3)_2O$) 2.60 (3H, s), 7.35 (1H, dd, J 2, 8), 7.55 (1H, d, J 2), 7.85 (1H, d, J 8)	270 (48), 253 (100), 238 (48)
4l	M, 222.0455	M, 222.0463	270 (4.62), 325sh (3.73), 437 (3.54)	(($CD_3)_2SO$) 2.55 (3H, s), 3.80 (3H, s), 6.95 (1H, dd, J 2, 8), 7.30 (1H, d, J 8), 7.50 (1H, d, J 2)	222 (57), 205 (100), 190 (48), 149 (37)
4m	M, 222.0455	M, 222.0463	255 (4.47), 290sh (3.65), 395 (3.07)	(($CD_3)_2O$) 2.55 (3H, s), 3.90 (3H, s), 6.70 (1H, dd, J 2, 8), 6.90 (1H, d, J 2), 7.90 (1H, d, J 8)	222 (79), 201 (100), 190 (70), 149 (74)

a For bromo- and chloro-compounds only the lower isotope-containing peak is given.

solution was neutralised with hydrochloric acid and organic material extracted into ether, then, after drying the solution and evaporation, crude material was purified by chromatography over

silica, eluting with $CHCl_3$/EtOH (95:5), to give the 5-fluoro- (89%) and 5-chloro- (87%) -isatin oximes identified by comparisons with authentic samples.[16]

ACKNOWLEDGEMENT

We thank Fine Organics Ltd., Middlesborough, U. K. for wholly supporting this work, including supplying 1,1-bis(methylthio)-2-nitroethene.

REFERENCES

1 S. P. Hiremath and M. Hooper, *Adv. Heterocycl. Chem.*, **1978**, *22*, 123.
2 L. Kalb and J. Bayer, *Ber.*, **1912**, *45*, 2150.
3 J. van Alpen, *Recl. Trav. Chim.*, **1941**, *60*, 138.
4 J. Grimshaw and W. G. Begley, *Synthesis*, **1974**, 496.
5 W. C. Sumpter, *Chem. Rev.*, **1944**, *34*, 407; F. D. Popp, *Adv. Heterocycl. Chem.*, **1975**, *18*, 1.
6 J. Harmenberg, B. Wahren, J. Bergman, S. Åkerfeldt, and L. Lundblad, *Antimicrob. Agents Chemother.*, **1988**, *32*, 1720.
7 A. H. Jackson, *Chem. Ind.*, 1965, 1652; B. L. Mylari, T. J. Carty, P. F. Moore, and W. J. Zembrowski, *J. Med. Chem.*, **1990**, *33*, 2019.
8 G. Bargellini, C. J. Turi, *Gazz. Chim. Ital.*, **1954**, *84*, 157; G. R. Bedford, M. W. Partridge, *J. Chem. Soc.*, **1959**, 1633; J. B. Campbell, T. V. Davenport, *Synth. Commun.*, **1989**, *19*, 2255
9 C.-C. Cheng and S.-J. Yan, *Organic Reactions*, **1982**, *28*, 37.
10 L. Baiocchi and M. Giannangeli, *J. Heterocycl. Chem.*, **1988**, 1905.
11 See for example T. W. Stiles and D. McNeil, *Tetrahedron Lett.*, **1990**, *31*, 7277.
12 M. S. Gil-Turnes, M. E. Hay, and W. Fenical, *Science*, **1989**, *246*, 116.
13 For recent examples see D. St. C. Black, D. J. Brockway, and G. I. Moss, *Austr. J. Chem.*, **1986**, *39*, 1231.
14 B. Goodwin, *Chem. Brit.*, **1988**, 336; R. Gandy and M. G. Hill, *Chem. Brit.*, **1988**, 336.
15 K. Wiechert, H.-H. Heilmann, and W. Jacob, *Z. Chem.*, **1961**, *6*, 191.
16 T. Kearney, A. Jackson, and J. A. Joule, *Synthesis*, **1991**, in press.
17 *cf.* T. Ohwada, T. Ohta, and K. Shudo, *J. Am. Chem. Soc.*, **1986**, *108*, 3029; K. Okabe. T. Ohwada, T. Ohta, and K. Shudo, *J. Org. Chem.*, **1989**, *54*, 733 and references therein; J.-M. Coustard, J.-C. Jacquesy, and B. Violeau, *Tetrahedron Lett.*, **1991**, *32*, 3075.

Received, 11th November, 1991