Facile Syntheses of Oxindoles and 3-Oxo-1,2,3,4-tetrahydroisoquinolines

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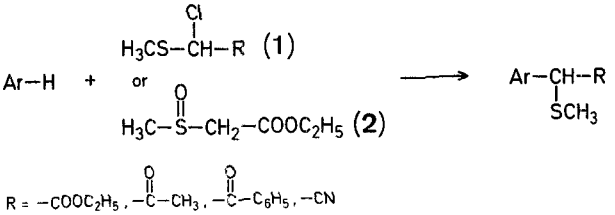
In previous papers[1,2], we reported that alkoxycarbonyl-, acyl-, and cyano-substituted methylthiomethyl groups can be easily introduced into aromatic rings by two methods:

- Friedel-Crafts reaction of the arene with alkoxycarbonyl-, acyl-, or cyano-substituted chloromethyl methyl sulfides **(1)**;
- reaction of the arene with the intermediate of the Pummerer reaction of ethyl methylsulfinylacetate **(2)** and *p*-toluenesulfonic acid.



We now report an application of these methods to the synthesis of oxindoles **(15)** and 3-oxo-1,2,3,4-tetrahydroisoquinolines [**16**, 1,4-dihydro-3(2*H*)-isoquinolinones].

For example, *N*-methyloxindole **(15b)** was synthesized by the following two procedures:

Method A: *N*-Acylation of *N*-methylaniline **(3b)** with α-chloro-α-(methylthio)-acetyl chloride **(5)** in dichloromethane followed by Friedel-Crafts cyclization of the resultant α-chloro-α-methylthio-*N*-methylacetanilide **(7b)** to lactam **13b** (94%) and demethylsulfenylation of **13b** to **15b** (76%) with Raney nickel[3].

Method B: *N*-Acylation of *N*-methylaniline **(3b)** with α-(methylthio)-acetyl chloride[4] **(6)** followed by oxidation of the resultant α-(methylthio)-*N*-methylacetanilide **(9b)** with 3-chloro-

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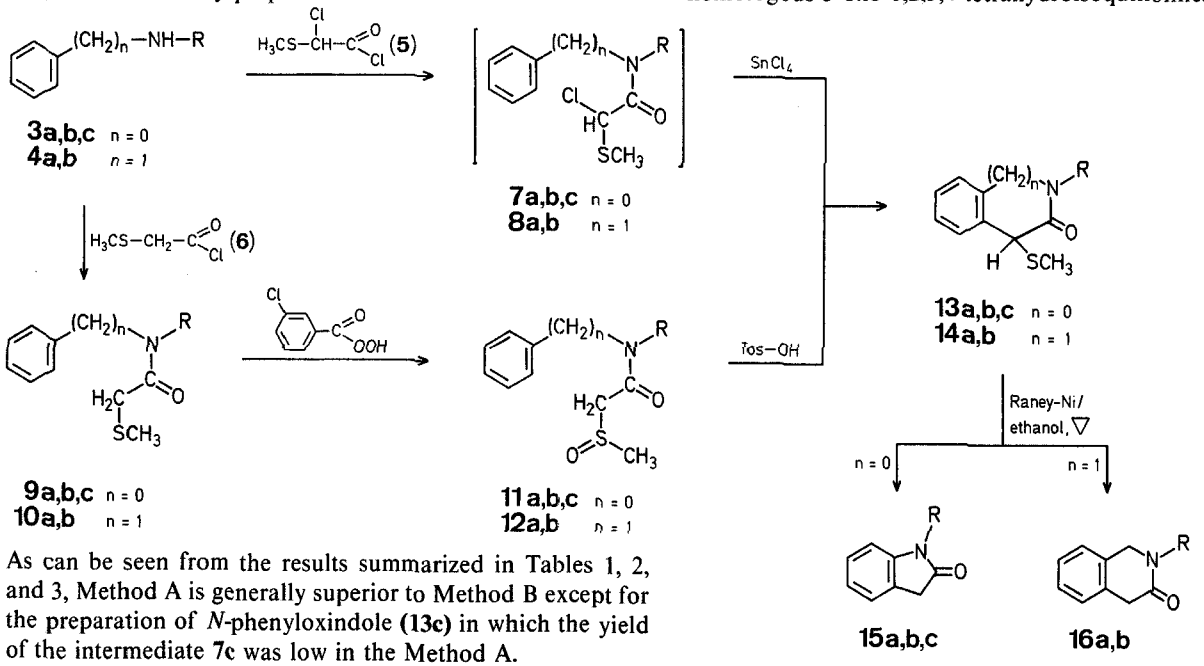
benzoperoxoic acid[2] to give *N*-methyl-(methylsulfinyl)-acetanilide **(11b)**. Treatment of sulfoxide **11b** with 2 equivalents of *p*-toluenesulfonic acid in boiling carbon tetrachloride gives lactam **13b** in 82% yield.

The oxindoles **15a, c** and tetrahydroisoquinoline derivatives **16a, b** were similarly prepared.



As can be seen from the results summarized in Tables 1, 2, and 3, Method A is generally superior to Method B except for the preparation of *N*-phenyloxindole **(13c)** in which the yield of the intermediate **7c** was low in the Method A.

Of the several methods reported for syntheses of oxindoles from the corresponding anilines[5], the most simple and general one is the intramolecular cyclization of α-haloacetanilides via Friedel-Crafts reaction using aluminum chloride[6]. However, this method requires high temperatures (~200°C). The synthesis of 3-oxo-1,2,3,4-tetrahydroisoquinolines from the corresponding benzylamines can be achieved via cyclization of *N*-benzyl-α-chloroacetamides but it requires photochemical conditions[7]. The preparation of **15** and **16** described here can be performed under mild conditions, affords satisfactory yields, and thus may provide a useful route to oxindoles **(15)** and the homologous 3-oxo-1,2,3,4-tetrahydroisoquinolines **(16)**.

α-Chloro-α-(methylthio)-acetyl Chloride (5):

N-Chlorosuccinimide (10.73 g, 90.3 mmol) is added in small portions to a stirred solution of α-(methylthio)-acetyl chloride[4] (**6**; 10 g, 80.3 mmol) in thionyl chloride (10 ml) at room temperature. The mixture is stirred for 30 min, succinimide that separates is removed by filtration,

Table 1. α-(Methylthio)-acetamides (**9** and **10**) and Methylsulfinylacetamides (**11** and **12**)

Product	R	Yield [%]	m.p. [°C] (solvent) or b.p. [°C]/torr	Molecular[a] formula	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
9a	H	78	78–78.5° (benzene/hexane)	$C_9H_{11}NOS$ (181.2)	3320 (NH), 1670 (CO)	2.19 (s, 3H); 3.32 (s, 2H); 6.9–7.7 (m, 5H); 8.4–8.9 (br, 1H)
9b	CH_3	96	150–160°/4	$C_{10}H_{13}NOS$ (195.2)	1640 (CO)	2.18 (s, 3H); 3.04 (s, 2H); 3.29 (s, 3H); 7.0–7.6 (m, 5H)
9c	C_6H_5	96	68–68.5° (hexane)	$C_{15}H_{15}NOS$ (257.3)	1665 (CO)	2.26 (s, 3H); 3.17 (s, 2H); 7.32 (s, 10H)
10a	H	81	63–64° (benzene/hexane)	$C_{10}H_{13}NOS$ (195.2)	3410 (NH), 1665 (CO)	2.1 (s, 3H); 3.21 (s, 2H); 4.47 (d, 2H, J=6 Hz); 7.3 (s, 5H); 7.5–7.7 (br, 1H)
10b	CH_3	93	160–170°/2	$C_{11}H_{15}NOS$ (209.3)	1625 (CO)	2.22 (s, 3H); 2.97 (s, 3H); 3.31 (s, 2H); 4.59 (s, 2H); 7.0–7.5 (m, 5H)
11a	H	93	145–146° (acetone)	$C_9H_{11}NO_2S$ (197.2)	3310 (NH), 1675 (CO), 1030 (SO)	2.77 (s, 3H); 3.65 (ABq, 2H, J=14 Hz); 7.0–7.8 (m, 5H); 9.1 (br, 1H)
11b	CH_3	85	91.5–93.5° *(benzene)*	$C_{10}H_{13}NO_2S$ *(211.2)*	1640 (CO), *1050 (SO)*	2.73 (s, 3H); 3.3 (s, 3H); 3.59 (ABq, 2H, J=14 Hz); 7.1–7.7 (m, *5H)*
11c	C_6H_5	94	64–65° (benzene)	$C_{15}H_{15}NO_2S$ (273.3)	1685 (CO), 1040 (SO)	2.80 (s, 3H); 3.75 (s, 2H); 7.35 (s, 10H)
12a	H	87	102–103° (benzene)	$C_{10}H_{13}NO_2S$ (211.2)	3480 (NH), 1675 (CO), 1030 (SO)	2.60 (s, 3H); 3.49 (ABq, 2H, J=14 Hz); 4.46 (d, 2H, J=6 Hz); 7.29 (s, 5H); 6.9–7.5 (br, 1H)
12b	CH_3	93	oil	$C_{11}H_{15}NO_2S$ *(225.3)*	1640 (CO), *1035 (SO)*	2.71, 2.74 (2s, 3H); 2.96, 2.98[b] (2s, 3H); 3.86, 3.89 (2s, 2H); 4.57, 4.60 (2s, 2H); 7.0–7.6 (m, 5H)

[a] All crystalline products gave satisfactory microanalyses: C, ±0.32; H, ±0.06; N, ±0.19. Oily products gave satisfactory high resolution mass spectra; **9b**: calc. 195.0716, found 195.0713; **10b**: calc. 209.0872, found 209.0857; **12b**: calc. 225.0824, found 225.0827.

[b] Separation of the signals is due to the presence of diastereoisomers.

Table 2. 3-(Methylthio)-oxindoles (**13**) and 4-Methylthio-3-oxo-1,2,3,4-tetrahydroisoquinolines (**14**)

Product	R	Yield [%]		m.p. [°C] (solvent)	Lit. m.p. [°C] Molecular formula[c]	I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
		Method A[a]	Method B[b]				
13a	H	61	5	124.5–125.5° (hexane)	126–127°[3]	3450 (NH), 1710 (CO)	2.03 (s, 3H); 4.27 (s, 1H); 6.8–7.6 (m, 4H); 9.25 (br s, 1H)
13b	CH_3	94	82	86.5–87.5° (benzene)	87.5–88.5°[3]	1705 (CO)	2.03 (s, 3H); 3.21 (s, 3H); 4.21 (s, 1H); 6.6–7.5 (m, 4H)
13c	C_6H_5	56	86	64–65° (hexane)	$C_{15}H_{13}NOS$ (255.3)	1725 (CO)	2.18 (s, 3H); 4.40 (s, 1H); 7.0–7.6 (m, 9H)
14a	H	55	8	123.5–125° (benzene)	$C_{10}H_{11}NOS$ (193.2)	3410 (NH), 1665 (CO)	2.28 (s, 3H); 4.30 (dd, 1H, J=16 Hz, 5 Hz); 4.35 (s, 1H); 4.75 (d, 1H, J=16 Hz); 7.0–7.5 (m, 4H); 7.7 (br d, 1H)
14b	CH_3	91	79	58–59° (ether)	$C_{11}H_{13}NOS$ (207.2)	1645 (CO)	2.25 (s, 3H); 3.11 (s, 3H); 4.40 (s, 1H); 4.18 (d, 1H, J=16 Hz); 4.84 (d, 1H, J=16 Hz); 7.0–7.5 (m, 4H)

[a] Yields are based on **3** or **4**.
[b] Yields are based on **11** or **12**.
[c] The new compounds gave satisfactory microanalyses: C, ±0.21; H, ±0.18; N, ±0.21.

Table 3. *N*-Phenyloxindole (**15c**)[a] and 3-Oxo- and 2-Methyl-3-oxo-1,2,3,4-tetrahydroisoquinolines (**16a, b**)

Product	R	Yield [%]	m.p. [°C] (solvent)		I.R. ($CHCl_3$) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
			found	reported		
15c	C_6H_5	85	120–121° (benzene/pet. ether)	121°[8]	1720 (CO)	3.68 (s, 2H); 6.5–7.7 (m, 9H)
16a	H	86	150–151° (benzene)	149.5–150.5°[9]	3440 (NH), 1670 (CO)	3.57 (s, 2H); 4.48 (s, 2H); 7.0–7.4 (m, 4H); 7.79 (b, 1H)
16b	CH_3	83	68–69° (ether)	68–69°[10]	1635 (CO)	3.11 (s, 3H); 3.60 (s, 2H); 4.5 (m, 2H); 7.0–7.4 (m, 4H)

[a] The conversions **13a**→**15a** and **13b**→**15b** have been reported in Ref.[3].

and then thionyl chloride is evaporated off. The residue is distilled in vacuo to give **5**; yield: 10.5 g (82%); b.p. 46–48°C/10 torr.

$C_3H_4Cl_2OS$	calc.	C 22.66	H 2.53
(159.0)	found	22.56	2.40

I.R. (neat): ν=1795 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ=2.27 (s, 3H); 5.59 ppm (s, 1H).

α-(Methylthio)-acetamides 9 and 10; General Procedure:

α-(Methylthio)-acetyl chloride (**6**; 3.74 g, 30 mmol) is added dropwise to a stirred solution of amine **3** or **4** (30 mmol) and triethylamine (3.04 g, 30 mmol) in dichloromethane (130 ml) at 0°C. The mixture is stirred at room temperature for 30 min or refluxed for 3 h (**9c**). Triethylamine hydrochloride that separates is removed by filtration and the filtrate is washed with dilute hydrochloric acid (20 ml) and water (30 ml), and dried with magnesium sulfate. The solvent is removed in vacuo and the residual solid or oil is recrystallized or distilled to give **9** or **10**.

Methylsulfinylacetamides 11 and 12; General Procedure:

3-Chlorobenzoperoxoic acid (85%; 5.08 g, 25 mmol) is added in small portions over 15 min to a stirred solution of α-(methylthio)-acetamide **9** or **10** (25 mmol) in dichloromethane (250 ml) at 0°C. After stirring at room temperature for 1 h, the mixture is washed with saturated sodium hydrogen carbonate (2×20 ml) and dried with magnesium sulfate. The solvent is removed in vacuo and the residual solid or oil (**12b**) is recrystallized or chromatographed on silica gel using ethyl acetate as an eluent to give **11** or **12**.

3-(Methylthio)-oxindoles (13) and 4-Methylthio-3-oxo-1,2,3,4-tetrahydroisoquinolines (14); General Procedures:

Method A: A solution of α-chloro-α-(methylthio)-acetyl chloride (**5**; 1.59 g, 10 mmol) in dry dichloromethane (10 ml) is added dropwise to a stirred solution of amine **3** or **4** (10 mmol) and triethylamine (1.01 g, 10 mmol) in dry dichloromethane (30 ml) at 0°C. Stirring is continued at room temperature for 15 min and then, tin(IV) chloride (3.13 g, 12 mmol) is added in one portion. The mixture is stirred at room temperature for an additional 30–50 min, and then quenched with ice/water (10 ml). The organic layer is washed with water (2×5 ml), and dried with magnesium sulfate. The solvent is removed in vacuo and the residue is chromatographed on silica gel using benzene as an eluent to give **13** or **14**.

Method B: Methylsulfinylacetamide **11** or **12** (5 mmol) is heated under reflux in dry carbon tetrachloride (25 ml) containing anhydrous *p*-toluenesulfonic acid (1.72 g, 10 mmol) for 20 min. After cooling to room temperature, the mixture is washed with water (2×5 ml), dried with magnesium sulfate, and worked up as described above in Method A to give **13** or **14**.

***N*-Phenyloxindole (15c) and 3-Oxo-1,2,3,4-tetrahydroisoquinolines (16a, b); General Procedure:**

Compound **13c**, **14a**, or **14b** (1 mmol) is heated under reflux in ethanol (10 ml) containing Raney nickel (2 g) for 2 h. The Raney nickel is then removed by filtration and the solvent evaporated. The residual solid is recrystallized to give **15c**, **16a**, or **16b**.

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