Tandem Meinwald Rearrangement–Fischer Indolisation: A One-Pot Conversion of Epoxides into Indoles

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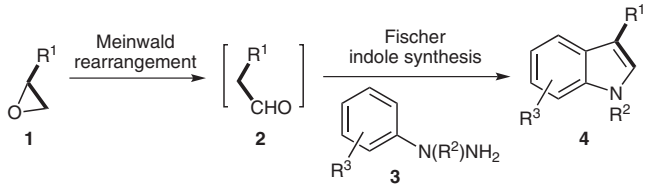
Abstract: A tandem $Sc(OTf)_3$-mediated Meinwald epoxide rearrangement–Fischer indole synthesis is reported. Optimisation and scope and limitation studies are described. In addition, preliminary investigations to develop a telescoped epoxidation–Meinwald rearrangement–Fischer indole sequence are outlined.

Key words: aldehydes, epoxides, indoles, rearrangements, tandem reactions

As part of our continuing interest in the design and development of tandem processes leading to heterocyclic systems,[1] we now report initial studies towards an epoxide rearrangement–indole forming sequence. The Meinwald rearrangement of epoxides to aldehydes and ketones[2] has received significant attention in recent years with effort focused on the discovery of systems which are both catalytic in Lewis acid and selective in the formation of either aldehydes[3a–c] or ketones.[3a,4] Whilst the Meinwald rearrangement has been widely exploited in natural product synthesis,[5] there have been fewer reports of tandem processes in which the resulting aldehyde is trapped in situ.[6] Such a process would be particularly valuable when the intermediate carbonyl compound is inaccessible or difficult to handle.

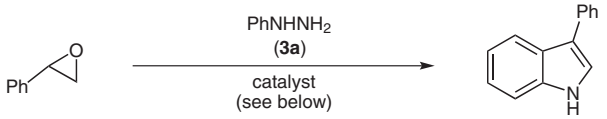
Given the prevalence of the indole structure in biologically active molecules,[7] we decided to investigate the possibility of combining the Meinwald rearrangement and the Fischer indole synthesis[8] into a tandem process (Scheme 1). Such a procedure seemed potentially viable given that both the Meinwald rearrangement and Fischer indole synthesis are mediated by mineral or Lewis acids.



Scheme 1

In order to explore the viability of the tandem sequence shown in Scheme 1, we first investigated the reaction between styrene oxide (**1a**) and phenylhydrazine (**3a**) to give 3-phenylindole (**4a**, Table 1). Styrene oxide (**1a**) was chosen as its rearrangement to phenyl acetaldehyde (**2a**) is well documented.[9] The Fischer indole synthesis of indole **4a** from phenyl acetaldehyde (**2a**) and phenylhydrazine (**3a**) is also known.[10]

Table 1 Preliminary Studies on the Conversion of Styrene Oxide (**1a**) into 3-Phenylindole (**4a**)[a]



Entry	Catalyst	Yield (%)
1	$BF_3{\cdot}OEt_2$	16
2	$Zn(OTf)_2$	21
3	$CuOTf{\cdot}C_6H_6$	25
4	AgOTf	36
5	$Bi(OTf)_3$	36
6	$Sc(OTf)_3$	51 (57)[b]

[a] Epoxide (0.9 mmol), hydrazine (0.9 mmol), Lewis acid (0.5 equiv), THF (2 mL), Ace pressure tube, 100 °C (oil bath), 1 h.
[b] Yield in the presence of 3 Å MS.

The first trial experiment used THF as solvent with boron trifluoride diethyl etherate as Lewis acid and we were delighted to obtain the desired indole **4a**, albeit in low yield (Table 1, entry 1). Several other Lewis acidic metal halides (e.g., $ZnCl_2$, $ZrCl_4$, $SnCl_2{\cdot}2H_2O$, and $MgBr_2$) were evaluated but were found to be poor catalysts for the reaction as were lithium tetrafluoroborate and copper(II) tetrafluoroborate. Protic acids were also investigated, but were unsuccessful. Metal triflates, however, were much more efficient (entries 2–6) with commercial $Sc(OTf)_3$ by far the best (51%, entry 6).

Further optimisation of the scandium(III) triflate process was then carried out. It was established that a minimum loading of 50 mol% of scandium(III) triflate was required to achieve the optimum reaction efficiency (with a molar equivalent the yield was essentially unchanged at 52%). In terms of hydrazine **3a**, an equimolar amount was optimal; the use of an excess (1.5 equiv) led to a reduction in the yield of indole **4a** to 25%. Then, following a report by

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Kobayashi's group that the addition of dehydrating agents increased the yield of $Yb(OTf)_3$-catalysed Pictet–Spengler reactions,[11] we found that the addition of 3 Å molecular sieves gave a small increase in yield of indole **4a** to 57%. In the final set of optimisation experiments, the reaction solvent was investigated; ethereal and chlorinated solvents are commonly used for the Meinwald rearrangement, whereas the Fischer indole synthesis is usually conducted in alcoholic solution or neat acid. For the tandem Meinwald rearrangement–Fischer indole sequence several solvent types were examined but none offered an improvement in yield over THF.

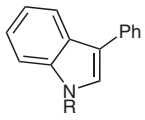
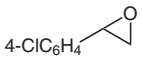
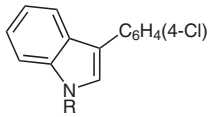
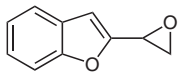
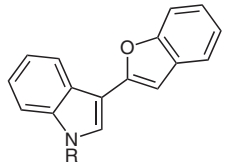
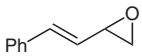
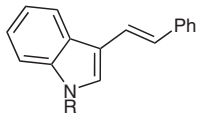
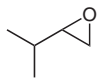
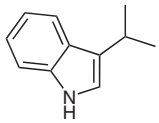
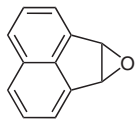
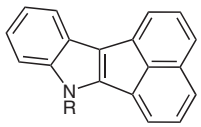
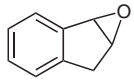
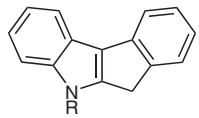
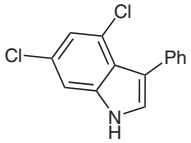
Having established a robust practical procedure for the tandem Meinwald epoxide rearrangement–Fischer indole synthesis using styrene oxide and phenylhydrazine, we went on to explore the scope and limitations of the process in terms of both epoxide and hydrazine substrate (Table 2). First, the reactions of styrene oxide (**1a**) with phenylhydrazine (**3a**) and 1-methyl-1-phenylhydrazine (**3b**) were compared (entry 1). As can be seen, the reaction with **3b** to produce the *N*-methylindole (**4b**) proceeded in excellent yield (85%), presumably reflecting the more efficient trapping of the intermediate phenylacetaldehyde (**2a**, which is known to readily undergo aldol condensation and also to trimerise) by the more nucleophilic hydrazine.[12] For this reason, the reactions of both phenylhydrazine (**3a**) and 1-methyl-1-phenylhydrazine (**3b**) were explored with the substrates **1b**–**g** (entries 2–7).

Initially, epoxides which rearrange to intermediate aldehydes were investigated. As can be seen from Table 2, in addition to styrene oxide, two other aryl epoxides also underwent the tandem Meinwald epoxide rearrangement–Fischer indole synthesis. 4-Chlorostyrene oxide (**1b**) gave the indoles **5a** and **5b**[13] in moderate to high yields via the unstable intermediate 4-chlorophenylacetaldehyde (entry 2). Benzofuranyl epoxide (**1c**) gave the novel bisheterocycles **6a** and **6b**, albeit in low yields (entry 3);[14] to the best of our knowledge, this is the first example of the Meinwald rearrangement of a heteroaryl-substituted epoxide.

Moving on from aryl epoxides, the vinyl and alkyl variants **1d** and **1e** were studied (entries 4 and 5). With epoxide **1d**, the expected indole products **7a** and **7b** were isolated in low yields only, possibly due to the sensitivity of the highly unstable γ,δ-unsaturated aldehyde intermediate. In the case of *iso*-propyloxirane (**1e**) no trace of indole formation was observed and this was the case with other aliphatic epoxides also, indicating a current limitation of the tandem process.

Epoxides which rearrange to aryl ketones were studied next and these performed well in the tandem Meinwald epoxide rearrangement–Fischer indole sequence. Thus, acenaphthylene oxide (**1f**) gave the highly coloured pentacyclic indoles **9a** and **9b** in 56% and 63% yield, respectively (entry 6). With indene oxide (**1g**) and phenylhydrazine (**3a**), indole **10a** was obtained in 36% yield; though moderate, this yield reflects the propensity of the Meinwald rearrangement product, 2-indanone, to undergo

Table 2 Scope and Limitations of the Tandem Sequence

Entry	Reactants		Products (yield, %)[a,b]	
1	**1a**			
	3a	$PhN(H)NH_2$	**4a**	R = H (57)
	3b	$PhN(Me)NH_2$	**4b**	R = Me (85)
2	**1b**			
	3a		**5a**	R = H (52)
	3b		**5b**	R = Me (81)
3	**1c**			
	3a		**6a**	R = H (21)
	3b		**6b**	R = Me (31)
4	**1d**			
	3a		**7a**	R = H (10)
	3b		**7b**	R = Me (13)[c]
5	**1e**			
	3a		**8a**	R = H (0)
	3b		**8b**	R = Me (0)
6	**1f**			
	3a		**9a**	R = H (56)
	3b		**9b**	R = Me (63)
7	**1g**			
	3a		**10a**	R = H (36)
	3b		**10b**	R = Me (70)[c,d]
8	**1a**			
	3c	$3,5\text{-}Cl_2C_6H_3N(H)NH_2$	**11**	(61)[e]

[a] Unless stated otherwise all reactions were conducted with epoxide (1.0 equiv), hydrazine (1.0 equiv), $Sc(OTf)_3$ (0.5 equiv), 3 Å MS, THF, Ace pressure tube, 100 °C, 1 h.
[b] All yields refer to isolated material after flash column chromatography.
[c] $Sc(OTf)_3$ was added at 0 °C to minimise the exotherm.
[d] The product was found to be unstable to SiO_2 and was therefore purified on Florisil® (200 mesh).
[e] The reaction required heating at 150 °C for 3 h to reach completion.

aldol self-condensation (for example, under the conditions employed by Sainsbury et al. the Fischer synthesis of indole **10a** from 2-indanone proceded in only 8% yield).[15a] The isolation of *N*-methylindole **10b** from indene oxide (**1g**) and hydrazine **3b** in 70% yield is also noteworthy as the Fischer method for the synthesis of indole **10b** directly from 2-indanone afforded **10b** in only 59% yield.[15b]

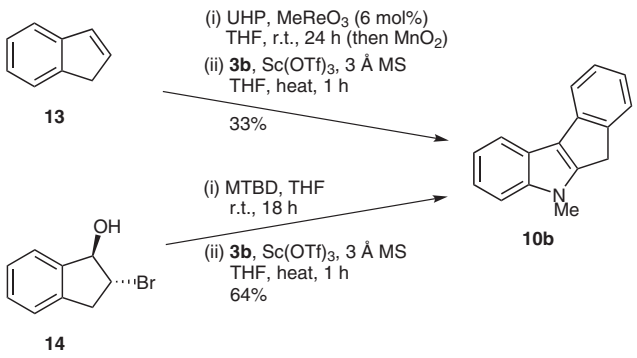
The final example in Table 2 (entry 8) illustrates that by replacing phenylhydrazine (**3a**) with arylhydrazines such as **3c**, aryl-substituted indoles such as the novel doubly chlorinated example **11** can be prepared.

This reaction required more vigorous conditions (150 °C for 3 h), presumably as a consequence of the additional steric and electronic perturbations of the [3,3]-sigmatropic rearrangement.

In all of the examples in Table 2, the use of 1-methyl-1-phenylhydrazine (**3b**) resulted in higher, often significantly higher, yields. However, the demethylation of *N*-methylindoles is not well precedented. We therefore carried out the tandem rearrangement on styrene oxide **1a** using 1-benzyl-1-phenylhydrazine (**3d**, Scheme 2). This process gave the *N*-benzylated indole **12** in good yield. Debenzylation to produce 3-phenylindole (**4a**) was then carried out using a published procedure, involving treatment with KO*t*-Bu and oxygen.[16] Although unoptimised, the sequence in Scheme 2 illustrates the potential of the Meinwald epoxide rearrangement–Fischer indole methodology to directly generate indoles with a removable N-protecting group.

In principle it should be possible to further extend this novel tandem process by the in situ generation of the epoxide prior to the Meinwald rearrangement–Fischer indole sequence. Scheme 3 illustrates two preliminary experiments which confirm the viability of such an approach.

Thus, indene oxide (**1g**) was formed by the methyltrioxorhenium-catalysed[17] urea–hydrogen peroxide (UHP) epoxidation of indene **13** (MnO_2 was subsequently added to quench excess UHP). Then, in the same 'pot', 1-methyl-1-phenylhydrazine (**3b**) and scandium triflate were added to effect the Meinwald rearrangement–Fischer indole sequence giving tetracyclic indole **10b**. The same product was prepared by starting with the readily available bromohydrin (**14**) which was treated with 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) to generate indene oxide (**1g**) in situ, with further elaboration giving indole **10b**. These procedures combine three steps (epoxide formation–Meinwald rearrangement–Fischer indole synthesis) into a one-pot process and avoid the need to directly handle epoxides. Further optimisation is required but the potential of these telescoped procedures has been clearly established.



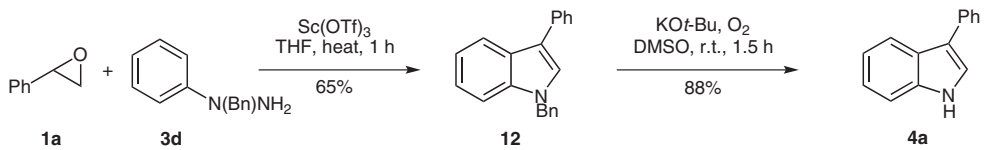
Scheme 3

In summary, we have developed a tandem Meinwald rearrangement–Fischer indole sequence for the direct conversion of epoxides into indoles thereby avoiding the need to handle the intermediate carbonyl compounds. The process has been shown to be compatible with a range of substituted aryl epoxides and phenylhydrazines allowing for the formation of indoles functionalised at nitrogen, on the aryl substituent, and on the indole carbocycle. Finally, preliminary experiments indicate that the sequence can be further telescoped with epoxide formation to achieve a one-pot preparation of indoles directly from an alkene or bromohydrin. The development of other tandem processes in combination with the Meinwald rearrangement is under way and will be reported in due course.

Representative Experimental Procedure

Preparation of 3-(4′-Chloro-phenyl)-1-methylindole (5b)

1-Methyl-1-phenylhydrazine (**3b**, 103 μL, 0.88 mmol, 1.0 equiv) and powdered $Sc(OTf)_3$ (216 mg, 0.44 mmol, 0.5 equiv) were added to a mixture of 2-(4-chlorophenyl) oxirane (**1b**, 106 μL, 0.88 mmol, 1.0 equiv) and activated 3 Å MS (150 mg) in anhyd THF (2 mL) in an Ace pressure tube under argon. The resulting mixture was heated to 100 °C over 10 min and maintained at this temperature for 1 h. The cooled reaction mixture was then diluted with sat. aq $NaHCO_3$ (10 mL), extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was pre-adsorbed on to SiO_2 and purified by silica flash column chromatography eluting with PE–acetone (50:1) to afford indole **5b** (171 mg, 0.71 mmol, 81%) as a pale yellow solid, which was recrystallised from PE to afford pale yellow plates mp 95–96 °C (lit.[13] mp 96.6–97 °C); which gave fully consistent ^{1}H NMR, ^{13}C NMR, and IR data.



Scheme 2

Acknowledgment

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3-(2′-Benzofuranyl) indole (6a)

Pale orange microcrystals; mp 162–163 °C (heptane); R_f = 0.27 (PE–Et_2O, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (br s, 1 H), 8.05–8.00 (m, 1 H), 7.71 (d, *J* = 2.5 Hz, 1 H), 7.57–7.52 (m, 1 H), 7.49–7.45 (m, 1 H), 7.44–7.39 (m, 1 H), 7.29–7.24 (m, 2 H), 7.23–7.16 (m, 2 H), 6.91 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 152.9, 136.6, 129.9, 124.6, 123.3, 123.12, 123.08, 122.8, 121.1, 120.4, 120.3, 111.7, 110.8, 108.8, 99.7. IR (neat): ν_{max} = 3399, 2918, 2850, 1623, 1453, 1427, 1358, 1249, 1100 cm^{-1}. MS (EI$^+$): *m/z* (%) = 233 (97) [M$^+$], 135 (38), 97 (37), 95 (50), 93 (37), 91 (52), 83 (37), 81 (63), 79 (50), 71 (51), 69 (71), 67 (100), 57 (73), 55 (91), 43 (48), 41 (52). HRMS (EI$^+$): *m/z* calcd for $C_{16}H_{11}NO$: 233.0841; Found: 233.0842 [M$^+$] (0.4 ppm error).

1-Methyl-3-(2′-benzofuranyl) indole (6b)

Colourless microcrystals; mp 109–110 °C (*i*-PrOH); R_f = 0.44 (PE–Et_2O, 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.62 (s, 1 H), 7.60–7.57 (m, 1 H), 7.54–7.49 (m, 1 H), 7.40 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.35 (app. td, *J* = 7.5, 1.5 Hz, 1 H), 7.31 (app. td, *J* = 7.5, 1.5 Hz, 1 H), 7.27–7.22 (m, 2 H), 6.91 (d, *J* = 0.5 Hz, 1 H) 3.85 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 153.1, 137.5, 130.0, 127.7, 125.1, 123.1, 122.8, 122.6, 120.7, 120.5, 120.1, 110.7, 109.9, 107.0, 99.1, 33.2. IR (neat): ν_{max} = 3053, 2924, 2853, 1624, 1609, 1468, 1452, 1371, 1254, 1203, 1156, 1088, 1014 cm^{-1}. MS (EI$^+$): *m/z* (%) = 247 (100) [M$^+$], 232 (26). HRMS (EI$^+$): *m/z* calcd for $C_{17}H_{13}NO$: 247.0997; found: 247.0987 [M$^+$] (4.0 ppm error). Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.39; H, 5.36; N, 5.57.

4,6-Dichloro-3-phenylindole (11)

Orange oil; R_f = 0.16 (PE–Et_2O, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (br s, 1 H), 7.50 (dd, *J* = 8.0, 1.5 Hz, 2 H), 7.42–7.36 (m, 3 H), 7.34 (d, *J* = 2.0 Hz, 1 H), 7.19 (d, *J* = 2.5 Hz, 1 H), 7.15 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 134.5, 131.0, 128.1, 127.6, 127.2, 126.9, 124.9, 122.3, 121.9, 119.5, 110.1. IR (neat): ν_{max} = 3417, 3079, 2921, 2851, 1601, 1546, 1474, 1423, 1393, 1188, 1129, 1105, 1076 cm^{-1}. MS (EI$^+$): *m/z* (%) = 263 (64) [^{37}Cl^{35}ClM$^+$], 261 (100) [^{35}Cl^{35}ClM$^+$], 199 (25). HRMS (EI$^+$): *m/z* calcd for $C_{14}H_9NCl_2$: 261.0112; found: 261.0108 [M$^+$] (1.5 ppm error)].

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