Application of Directed Metalation in Synthesis. Part 5:[1,2] Synthesis of Condensed Sulfur-Oxygen Heterocycle via Novel Anionic Rearrangement-Cyclisation

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Abstract: Introduction of the methyl sulfanyl function in the *ortho*-position to *O*-carbamate functionality under standard directed metalation condition was followed by side-chain deprotonation with *sec*-butyl lithium at –78 °C. Upon warming to room temperature, the deprotonated species underwent intramolecular anionic rearrangement to afford *N*,*N*-diethyl-2-hydroxyarylthioacetamides. The rearranged products were cyclised with hot glacial acetic acid to afford condensed oxathiin-2-ones in excellent yields.

Key words: directed metalation, anionic rearrangement, oxathiin-2-one

The importance of *O*-aryl *N*,*N*-diethyl carbamate as a directing metalating group (DMG),[3] is as much due to its high efficiency in directed *ortho*-lithiation,[4] which puts it at par with other powerful DMGs, as to the mild metalation conditions required in *O*-carbamate directed lithiation, in comparison to other oxygen based DMGs[3] and its ability to introduce an allyl function in the *ortho*-position without any need for transmetalation.[3]

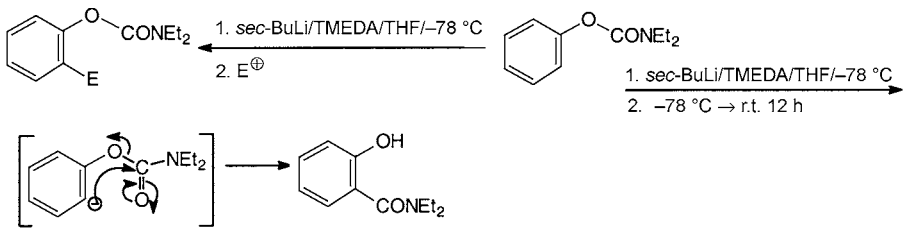
The utility of *O*-carbamate directed metalation can be seen in the generation of phenol,[3] when the product obtained by quenching the *ortho*-lithio derivative with electrophile, is subjected to alkaline hydrolysis or by subjecting to lithium aluminium hydride reduction followed by mild acidic work up, when the molecule does not contain any sensitive functional group. Another functional group interconversion, adding to the versatility of the process is the 1,3-carbamoyl migration, which takes place when the *ortho*-lithiated carbamate is warmed to room temperature in the absence of an electrophile (Scheme 1).

This is an anionic version of the *ortho*-Fries rearrangement,[3–5] which has been extensively used in synthesis.[3,6,7] The ubiquitous nature of this rearrangement is manifested in its several variations. Thus Gawley[8] has shown that *O*-benzyl carbamates with DMG participate in anionic rearrangement mediated by *sec*-BuLi or LDA. A remote anionic Fries rearrangement was reported by Snieckus[9] involving ring-to-ring carbamoyl transfer which provides general regioselective entries into sterically encumbered biaryls and substituted dibenzopyranones and fluorenones. A further important and useful variation of this rearrangement, the 'anionic homologus Fries rearrangement' was also reported by Snieckus (Scheme 2).[10] The rearrangement can lead to annelation of five membered rings as shown in the acid mediated cyclisation of the rearranged product leading to benzofuranone.

In this communication, we present here a hitherto unreported fourth variant of this carbamoyl transfer via intramolecular anionic rearrangement, which, like the other variations, provides new opportunities for regiospecific construction of aromatic building blocks from readily available starting materials. The rearrangement is shown in Scheme 3.

The starting *O*-carbamates **1** (Table 1) were prepared[11] from the corresponding phenols in near quantitative yield, by treatment with *N*,*N*-diethyl carbamyl chloride in the presence of sodium hydride in tetrahydrofuran.

The methyl sulfanyl group was introduced in to the position *ortho*- to the *O*-carbamate under standard directed metalation conditions.[3,12] Deprotonation was carried out with 2.5 molar equivalents of *sec*-BuLi and the *ortho*-



Scheme 1

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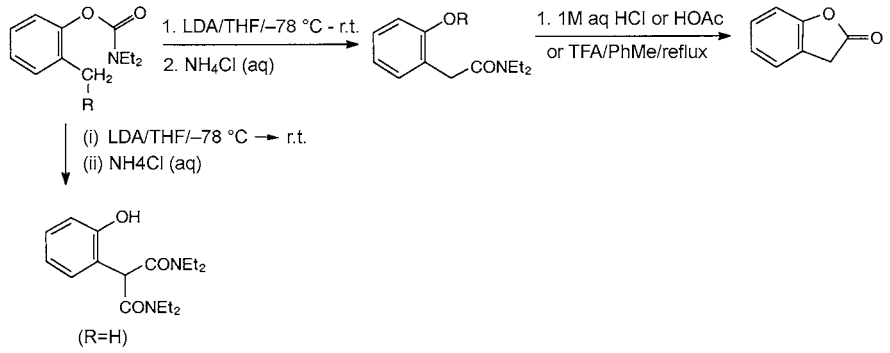
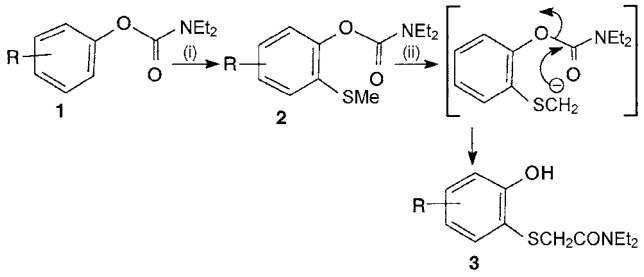
Art Id.1437-2096,E;2003,0,10,1474,1478,ftx,en;D09503ST.pdf.



Scheme 2

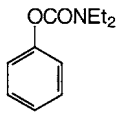
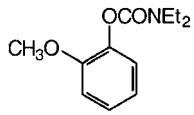
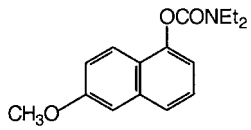
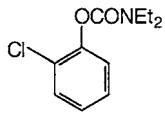
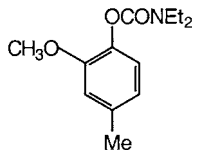


Scheme 3 *Reagents*: (i) *sec*-BuLi/TMEDA/THF/–78 °C/ MeS-SMe; (ii) *sec*-BuLi/TMEDA/THF/–78 °C to r.t.

lithio derivative was quenched with 2 molar equivalents of dimethyl disulfide (Table 2). In the ^{1}H NMR spectrum the signal due to the methyl sulfanyl function appeared as a three proton singlet around δ = 2.35 ppm, the corresponding signal in ^{13}C NMR was at δ = 42.5 ppm. Absorption due to carbonyl moiety changed from 1625 cm^{-1} to 1690 cm^{-1} in the starting carbamates to 1724 cm^{-1} to 1732 cm^{-1} after introduction of methyl sulfanyl function.

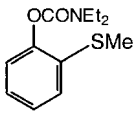
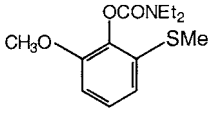
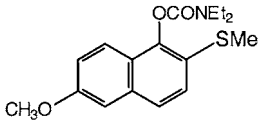
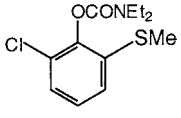
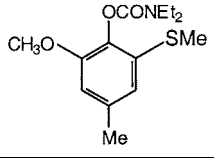
Our initial attempt to generate the SCH_2^- anion by treating compound **2** with LDA, led only to the recovery of the starting materials, which was surprising in view of our

Table 1 *O*-Aryl *N*,*N*-Diethyl Carbamates (**1**)

Entry	Compound	Mp[a] (°C)	Yield (%)
a		oil	96
b		oil	90
c		83–84	96
d		oil	94
e		51–53	95

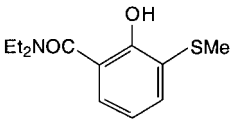
[a] Crystallised from EtOAc–light petrol and purified by column chromatography [eluant: EtOAc–light petrol (1:4)].

Table 2 *ortho*-Methyl Sulfanyl *O*-Aryl *N*,*N*-Diethyl Carbamates (**2**)

Entry	Compound	Mp[a] (°C)	Yield (%)
a		oil	92
b		65–67	81
c		64–65	84
d		oil	92
e		31–33	96

[a] Crystallised from EtOAc–light petrol and purified by column chromatography [eluant: EtOAc–light petrol (3:17)].

earlier success[13] in generating similar ions when the methyl sulfanyl group was present in the position *ortho*- to the $CONEt_2$ function. Use of *sec*-BuLi instead of LDA was however successful in generating the ion and upon allowing the reaction mixture to attain room temperature and maintaining at that temperature for 8–12 hours the expected anionic rearrangement resulted in *N*,*N*-diethyl-2-hydroxy phenyl thioacetamide (**3**).[14] The only exception was *N*,*N*-diethyl-1-carbamyloxy-2-methyl sulfanyl benzene (**2a**) which underwent 'normal' anionic *ortho*-Fries rearrangement to afford *N*,*N*-diethyl-2-hydroxy-3-methyl sulfanyl benzamide (**4**) (Figure 1).[15]



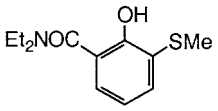
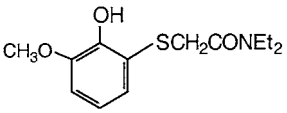
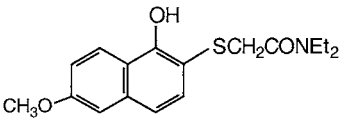
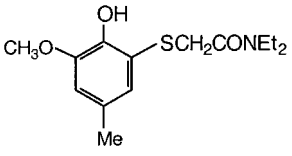
4

Figure 1

It may be conjectured that the reason behind the preferential ring deprotonation in this case, results from use of *sec*-BuLi. Kinetic deprotonation with LDA was not possible as we were unable to use this reagent (vide supra), presumably as to steric reasons. There being no free *ortho*-position in the other compounds examined, the anionic rearrangement took place via SCH_2^- anion. The *N*,*N*-diethyl-2-hydroxy aryl thioacetamides (**3**) were obtained in very good to excellent yields (Table 3).

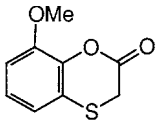
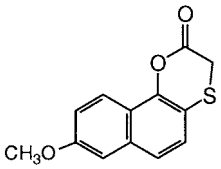
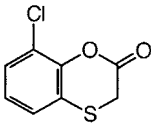
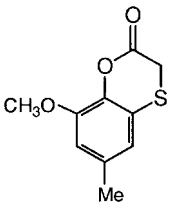
Heating the rearranged products with glacial acetic acid under reflux for 18–20 hours resulted in the annelation of [1,4]oxathiin ring on to the existing aromatic core (Table 4).[16] The suggested mechanistic pathway is shown in Scheme 4.

Table 3 *N*,*N*-Diethyl-2-hydroxy Aryl Thioacetamides (**3**)

Entry	Compound	Mp[a] (°C)	Yield (%)
a		56–58	89
b		low melting	93
c		low melting	90
d		low melting	85

[a] Crystallised from EtOAc–petroleum ether and purified by column chromatography [eluant: EtOAC:petroleum ether (3:7)].

Table 4 Annelated Oxathiin-2-ones (**5**)

Entry	Compound	Mp[a] (°C)	Yield (%)
a		68–71	82
b		82–84	84
c		94–96	81
d		117–121	83

[a] Crystallised from EtOAc–light petrol.

The present work represents a new and useful carbanionic rearrangement. While examples of such rearrangements abound in aliphatic chemistry,[17–19] their use in the synthesis of substituted aromatics is comparatively sparse, notable exceptions being those reported by Snieckus.[10]

Our approach is characterised by its simplicity and flexibility in comparison to earlier reported synthesis[20,21] of benz[1,4]oxathiin-2-ones. Work is in progress for the synthesis of a wider variety of this class of compounds.

Acknowledgement

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(1) Part 4, see: Mukherjee, C.; Kamila, S.; De, A. *Tetrahedron* **2003**, *59*, 4767.
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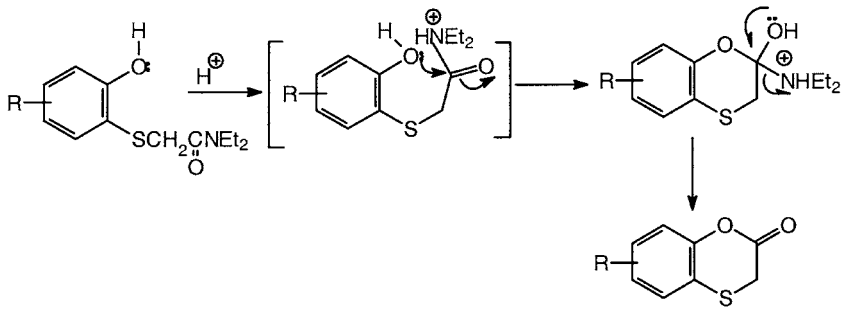

Scheme 4

(7) (a) Kamila, S.; Mukherjee, C.; De, A. *Tetrahedron Lett.* **2001**, *42*, 5955. (b) Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, 1339.

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(11) **Representative Example of Synthesis of *O*-Aryl *N*,*N*-Diethyl Carbamates.**
To a well stirred suspension of NaH (3 equiv), in anhyd THF (10 mL), a solution of 2-methoxy-4-methylphenol (28 mmol) in anhyd THF (10 mL) was added through a pressure equalising dropping funnel at r.t. After stirring the reaction mixture for 2 h, *N*,*N*-diethylcarbamylchloride (7.3 mL, 2 equiv) in THF (10 mL) was added to the reaction mixture. Stirring was continued for another 8 h. THF was removed in vacuo and usual aqueous work up afforded the crude product *N*,*N*-diethyl-1-carbamyloxy-2-methoxy-4-methylbenzene **1e** which was purified by crystallisation (EtOAc:petroleum ether). Colourless needles, 95% yield; mp 51–53 °C. IR (neat): 1720 (C=O) cm^{-1}. ^1H NMR (300 MHZ, $CDCl_3$): δ = 1.23 (t, 6 H, $-CH_2CH_3$), 2.34 (s, 3 H, $-CH_3$), 3.41 (q, 4 H, $-CH_2CH_3$), 3.8 (s, 3 H, -OMe), 6.74 (dd, 1 H, *J* = 3.0, 8.0 Hz, Ar-5H), 6.76 (d, 1 H, *J* = 3.0 Hz, Ar-3H), 6.96 (d, 1 H, *J* = 8.0 Hz, Ar-6H). ^{13}C (75 MHZ, $CDCl_3$): δ = 13.2, 13.8, 14.4, 21.8, 42.4, 42.5, 56.3, 113.7, 121.4, 123.2, 136.3, 138.7, 151.6, 154.7. Anal. Calcd for $C_{13}H_{19}O_3N$: C, 65.82; H, 8.01; N, 5.90. Found: C, 65.68; H, 7.87; N, 6.0.

(12) **Representative Example of Introduction of Methyl Sulfanyl Function by Directed Metalation.**
To a well stirred solution of TMEDA (5.5 mL, 2.5 equiv), anhyd THF (10 mL), *sec*-BuLi [26 mL of 1.4 M solution in cyclohexane, 2.5 equiv] kept at –78 °C under argon atmosphere, a solution of *N*,*N*-diethyl-1-carbamyloxy-2-methoxy-4-methylbenzene **1e** (14.5 mmol), in THF (5 mL) was added via syringe. After stirring for 30 min at that temperature, dimethyl disulfide (3.3 mL, 2.5 equiv) was added and stirring continued for further 45 min at the same temperature. The reaction mixture was then allowed to warm to r.t. and stirred for 10 h. Usual ammonium chloride work up afforded the crude *N*,*N*-diethyl-1-carbamyloxy-2-methylsulfanylbenzene. Purification by crystallisation (EtOAc–petroleum ether) afforded *N*,*N*-diethyl-1-carbamyloxy-2-methylsulfanyl-4-methyl-6-methoxybenzene **2e**. Yellowish needles, 96% yield; mp 31–33 °C. IR (neat): 1724 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.25 (t, 6 H, $-CH_2CH_3$), 2.25 (s, 3 H, -Me), 2.33 (s, 3 H, -SMe), 3.35–3.37 (q, 4 H, $-CH_2CH_3$), 3.72 (s, 3 H, -OMe), 6.49 (d, 1 H, *J* = 1.6 Hz, Ar-5H), 6.53 (d, 1 H, *J* = 1.6 Hz, Ar-3H). ^{13}C (75 MHz, $CDCl_3$): δ = 14.0, 15.5, 22.1, 42.5, 56.5, 110.6, 118.6, 133.1, 135.7, 136.4, 152.1, 153.7. Anal. Calcd for $C_{14}H_{21}O_3NS$: C, 59.36; H, 7.42; N, 4.94. Found: C, 59.18; H, 6.99; N, 5.0.

(13) Mukherjee, C.; De, A. *Synlett* **2002**, 325.

(14) **Representative Example of Preparation of *N*,*N*-Diethyl-2-hydroxy Aryl Thioacetamide.**
To a stirred solution of TMEDA (0.54 mL, 2.5 equiv), *sec*-BuLi (2.01 mL of 1.8 M solution, 2.5 equiv). in anhyd THF (7 mL) kept at –78 °C in argon atmosphere, a solution of *N*,*N*-diethyl-1-carbamyloxy-2-methylsulfanyl-4-methyl-6-methoxybenzene **2e** (14.5 mmol), in dry THF (3 mL) was added via syringe. Stirring was continued for 1 h at that temperature, then the reaction mixture was allowed to attain r.t. and kept for 8 h. Ammonium chloride work up afforded crude material which was purified by crystallisation (EtOAc–petroleum ether) to obtain *N*,*N*-diethyl-2-hydroxy-3-methoxy-5-methylphenylthioacetamide **3d**, 85% yield. IR (KBr): 3120 (-OH), 1624 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, 6 H, $-CH_2CH_3$), 2.21 (s, 3 H, $-CH_3$), 3.30 (q, 4 H, $-CH_2CH_3$), 3.61 (s, 2 H, $-SCH_2-$), 3.82 (s, 3 H, -OMe), 6.65 (d, 1 H, *J* = 1.6 Hz, Ar-4H), 6.87 (d, 1 H, *J* = 1.6 Hz, Ar-6H). ^{13}C (75 MHz, $CDCl_3$): δ = 13.2, 14.58, 21.2, 39.3, 41.6, 42.7, 56.5, 114.5, 119.3, 128.2, 129.3, 146.6, 148.4, 169.3. Anal. Calcd for $C_{14}H_{21}O_3NS$: C, 59.36; H, 7.4; N, 4.9. Found: C, 59.4; H, 7.5; N, 5.1.

(15) **Synthesis of *N*,*N*-Diethyl-2-hydroxy-3-methyl Sulfanyl Benzamide.**
To a stirred solution of TMEDA (1.34 mL, 3 equiv) was added *sec*-BuLi (4.0 mL of 1.9 M solution in cyclohexane, 2.5 equiv) in anhyd THF (7 mL) kept at –78 °C in argon atmosphere, a solution of *N*,*N*-diethyl-1-carbamyloxy-2-methylsulfanylbenzene **2a** (3.0 mmol) in dry THF (3 mL) was added via syringe. Stirring was continued for 1 h at that temperature, then the mixture was allowed to attain r.t. and kept for 8 h. Ammonium chloride work up afforded crude *N*,*N*-diethyl-2-hydroxy-3-methyl sulfanyl benzamide **3a** which was purified by crystallisation (EtOAc–petroleum ether). Yellowish needles, 89% yield; mp 56–58 °C. IR (KBr): 3057 (-OH), 1604 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, 6 H, $-CH_2CH_3$), 2.34 (s, 3 H, -SMe), 3.37–3.45 (q, 4 H, $-CH_2CH_3$), 6.80 (dd, 1 H, *J* = 7.7, 7.7 Hz, Ar-4H), 7.07 (dd, 1 H, *J* = 1.3, 7.7 Hz, Ar-3H), 7.26 (dd, 1 H, *J* = 1.3, 7.7 Hz, Ar-5H). ^{13}C (75 MHz, $CDCl_3$): δ = 13.8, 16.9, 42.3, 119.7, 125.9, 126.04, 127.6, 131.6, 155.2, 170.7. Anal. Calcd for $C_{12}H_{17}O_2NS$: C, 62.88; H, 7.4; N, 6.1. Found: C, 63; H, 7.5; N, 6.2.

(16) **Representative Example of Preperation of Benz[1,4]oxathiin-2-ones:**
Hydroxy compound **3d** (0.88 mmol) was refluxed with glacial acetic acid (7 mL) for 18 h under magnetic stirring. After cooling, the reaction mixture was extracted with

CH_2Cl_2 (2 × 100 mL). The organic layer was washed with H_2O and dried (Na_2SO_4). Removal of solvent afforded crude 6-methyl-8-methoxy-benz[1,4]oxathiin-2-one **5d** which was purified by crystallisation (EtOAc–light petroleum), 83% yield; mp 117–121 °C. IR (KBr): 1759 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.3 (s, 3 H, $-CH_3$), 3.41 (s, 2 H, $-SCH_2-$), 3.85 (s, 3 H, -OMe), 6.63 (s, 1 H, Ar-5H), 6.69 (s, 1 H, Ar-7H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 29.1, 56.5, 112.1, 119.9, 120.7, 135.2, 138.6, 148.8, 163.1. Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.14; H, 4.76. Found: C, 57.2; H, 4.62.

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