Anionic *ortho*-Fries Rearrangement, a Facile Route to Arenol-Based Mannich Bases

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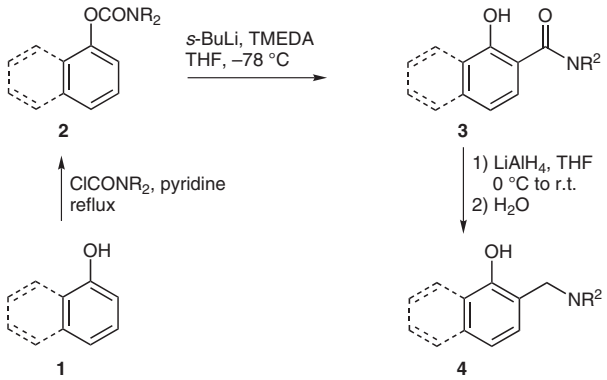
Received 31 July 2009

Abstract: Phenol and 1-naphthol-based carbamates undergo the anionic *ortho*-Fries rearrangement to their corresponding amides. Bulky substitution at position 8 of 1-naphthol-based carbamates makes the rearrangement an exclusive reaction, even at –90 °C, under a variety of conditions. The amides can be efficiently reduced to the corresponding Mannich bases. A novel route to 7-[(dialkylamino)methyl]-8-hydroxy-1-naphthaldehydes is presented.

Key words: rearrangements, reductions, Mannich bases, carbamates, *ortho*-Fries rearrangement

The Mannich reaction is an effective method for C–C bond formation and one of the fundamental reactions in organic synthesis.[1a] Recently Mannich bases have served as potential precursors to new BINOLAMS [2,2′-bis(aminomethyl)-1,1′-dihydroxy-4,4′-binaphthalenes],[1b] phase-transfer catalysts and chiral auxiliary ligands in asymmetric synthesis.[1c] They are also among the commonly used precursors to *o*-quinone methides.[1b] β-Amino ketones or esters that are versatile building blocks for N-heterocycles, can be prepared by this reaction.[2–4] Preformed iminium ions[5] allow the use of milder conditions. Lewis acid or transition-metal-catalysed variants have been reported.[6] The reaction has also been applied to phenols using various conditions and catalysts.[7] The anionic *ortho*-Fries rearrangement (otherwise known as the Snieckus rearrangement),[8] is a 1,3-acyl migration taking place on an aryl *O*-carbamate, a synthetically useful entity in its own right.[9] Its homologous version is also known[9a,10] and involves side chain deprotonation of *ortho*-alkyl-substituted congeners followed by intramolecular rearrangement. The resulting amides are potential precursors to Mannich bases through their reduction.[11]

We report herein, a facile route to phenol and 1-naphthol-based Mannich bases, making use of the anionic *ortho*-Fries rearrangement followed by reduction of the resulting amide, as the key operations. The delineated sequence integrates well-documented reactions. Thus, formation of *O*-carbamates **2**[12] is followed by their conversion to the amides **3**, which are eventually reduced to the Mannich bases **4** (Scheme 1, Tables 1 and 2).



Scheme 1 Synthesis of *O*-carbamates, amides and Mannich bases

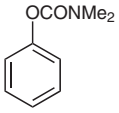
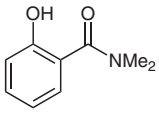
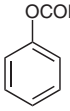
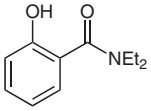
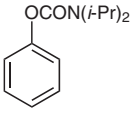
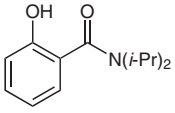
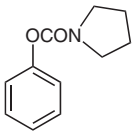
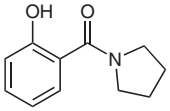
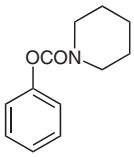
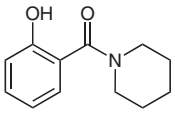
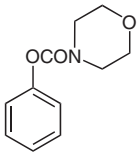
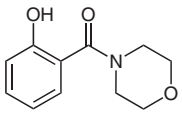
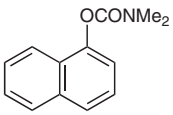
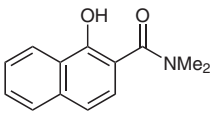
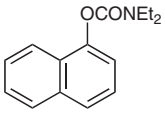
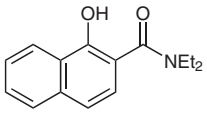
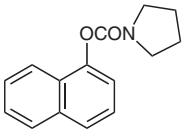
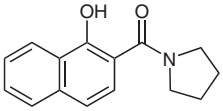
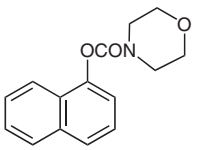
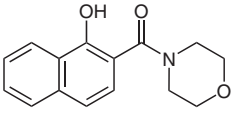
Interestingly, with carbamate **6**[29] substituted at position 8 with a bulky 1,3-dioxolane group, the anionic *ortho*-Fries rearrangement of **6** to **7** proceeds rapidly and exclusively, virtually in quantitative yield (88–92%), even at temperatures as low as –90 °C[30] (Scheme 2). The rearrangement takes precedence over any other *o*-derivatisation by a variety of electrophiles (benzaldehyde, benzoyl chloride, tetramethylsilyl chloride or methyl iodide) administered during the reaction.[31] Its dominance and ease of formation are attributed to a *peri*-interaction[32] taking place between the bulky groups in carbamates **6** while the relief of *peri*-strain provides the driving force. The reduction of amides **7** to the Mannich bases **8**,[33] without cleavage of the 1,3-dioxolane group, was accomplished using lithium aluminium hydride in tetrahydrofuran at 0 °C. Compounds **8** were hydrolysed to aldehydes **9**[34] by stirring with 10% aqueous HCl in THF at room temperature for 24 hours and then by adding 10% aqueous K_2CO_3 until pH 5. These reactions constitute a new route to 7-[(dialkylamino)methyl]-8-hydroxy-1-naphthaldehydes, available for further functionalisation.

The efficiency of reducing *N*,*N*-diethyl-1-hydroxy-2-naphthamide (Table 1, entry 8) to 2-[(diethylamino)methyl]-1-naphthol (Table 3, entries 1–4) was found to vary according to the conditions used. Powerful reducing agents, such as $LiAlH_4$ (entry 1)[21] or 9-BBN (entry 4),[35] reduced the amide to the amine at room temperature, in

SYNLETT 2009, No. 17, pp 2777–2782
Advanced online publication: 24.09.2009
DOI: 10.1055/s-0029-1217991; Art ID: D20609ST

short reaction times and in high yields. Equally effective was diphenylsilane under transition-metal-catalysed conditions (entry 3).[36] Weaker reducing agents such as $NaBH_4$ that require initial activation of the carbonyl group, for example by reaction with triflic anhydride (Tf_2O), were reduced through the intermediacy of an iminium ion.[5] Reaction of the amide with Tf_2O followed by $NaBH_4$ afforded the amine in only 40% yield while 40% of starting amide was recovered (entry 2).[37] In contrast reduction of its methyl ether derivative (Table 3, entries 5–7) was sluggish. With $LiAlH_4$ the amide was reduced to the amine in only 20% yield after 36 hours of reaction while 70% of starting amide was recovered (entry 5). Reaction of this amide with Tf_2O followed by $NaBH_4$

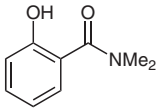
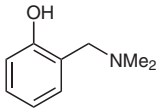
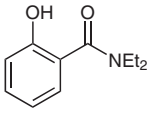
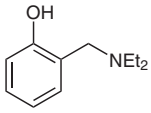
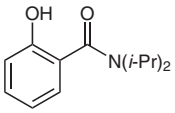
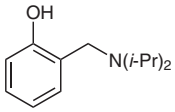
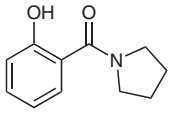
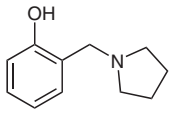
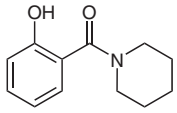
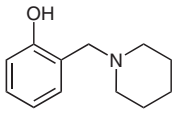
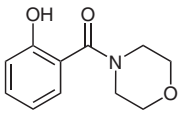
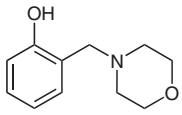
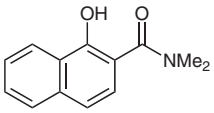
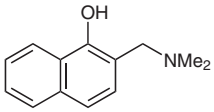
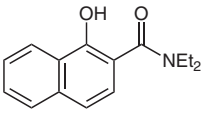
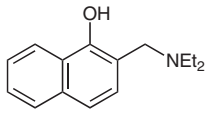
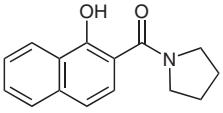
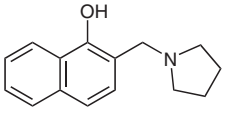
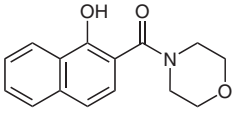
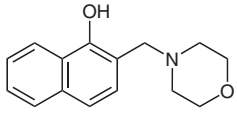
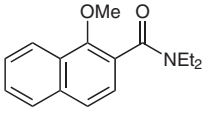
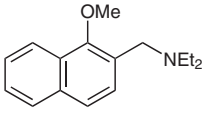
Table 1 Anionic *ortho*-Fries Rearrangement of Phenol and 1-Naphthol-Based Carbamates to Amides[13]

Entry	Substrate	Product[a]	Yield[b] (%)	Mp (°C) (Lit.)
1			75	165–166 (164–166.5)[14]
2			72	96–97 (93–97)[15]
3			78	162–163 (162–163)[16]
4			74	122–124 (118–124)[17]
5			76	141–143 (142–143)[18]
6			81	174–175 (175)[19]
7			73	164–165 (164–166.5)[13]
8			72	50–52[c]
9			65	93–95 (93–94)[18]
10			69	156–157 (155–157)[20]

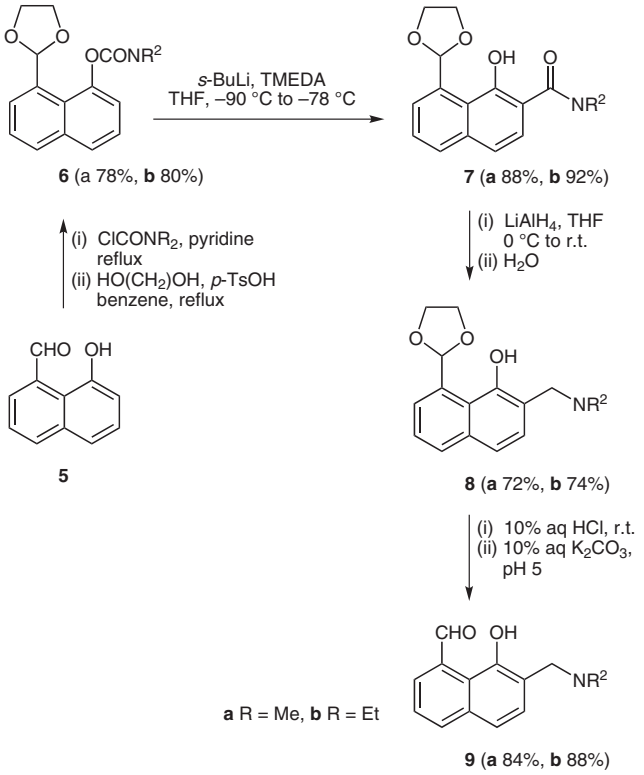
[a] Yields of the isolated pure compounds.
[b] The products were characterised by comparison of their mp, TLC, IR and ^1H NMR data with those of authentic samples.
[c] See experimental section.[13]

gave the amine in 15% yield while 50% of stating material was recovered (entry 6). Furthermore, reaction of the amide with Tf_2O followed by $LiAlH_4$ gave the amine in 40% yield while 35% of starting material was recovered (entry 7). These results suggest that the hydroxy group of the amides facilitates the reduction of the amide moiety through intramolecular hydrogen bonding to the adjacent carbonyl oxygen and, thus, activates the carbonyl group towards nucleophilic attack. In amides bearing a hydroxy group O-triflation is superseded by the intramolecular hydrogen bonding whereas in the methyl ether analogues it transpires that O-triflation is rather inefficient.

Table 2 Reduction of Amides to Mannich Bases[21]

Entry	Substrate	Product[a]	Yield (%)[b]	Mp or bp (°C)/Torr (Lit.)
1			75	99–100/12 (100–101/12)[22]
2			72	90–91/0.5 (89–92/0.5)[23]
3			78	oil[c,24]
4			74	oil[c,25]
5			76	31–32 (32–33)[26]
6			79	96–97 (95–97)[7c]
7			77	161–162 (160–162)[d,27]
8			65	149–150 (148–150)[d,27]
9			68	62–63 (63.5)[28]
10			74	80–82 (81–82)[27]
11			20	oil[c]

[a] Yields of the isolated pure compounds.
[b] The products were characterised by comparison of their mp, TLC, IR and ^1H NMR data with those of authentic samples.
[c] Compound decomposes rapidly.
[d] As hydrochloride salt.



Scheme 2 Transformation of 8-hydroxy-1-naphthaldehyde into 7-[(dimethyl or diethylamino)methyl]-8-hydroxy-1-naphthaldehyde

Table 3 Reduction of *N*,*N*-Diethyl-1-hydroxy(or methoxy)-2-naphthamide

Entry	R	Conditions[a–e]	Yields (%)[f]
1	H	A	79
2	H	B	40 (40)[g]
3	H	C	83
4	H	D	89
5	Me	A	20 (70)[g]
6	Me	B	15 (50)[g]
7	Me	E	40 (35)[g]

[a] Conditions A: (i) $LiAlH_4$, THF, 0 °C to r.t.[21]
[b] Conditions B: (i) TF_2O, pyridine, CH_2Cl_2, –40 °C; (ii) $NaBH_4$, –40 °C to r.t.[37]
[c] Conditions C: (i) Ph_2SiH_2, $RhH(PPh_3)_4$, THF, r.t.[36]
[d] Conditions D: 9-BBN, THF, r.t.[35]
[e] Conditions E: (i) TF_2O, pyridine, CH_2Cl_2, –40 °C; (ii) $LiAlH_4$, –40 °C to r.t.[37]
[f] Yields of the isolated pure compounds.
[g] The numbers in parentheses indicate the yield of the recovered starting amide.

In conclusion, a facile route to Mannich bases has been developed from phenol- and 1-naphthol-based carbamates via the anionic *ortho*-Fries rearrangement to amides, followed by reduction. A useful new route to 7-[(dialkylamino)methyl]-8-hydroxy-1-naphthaldehydes is provided. These easily performed, low-temperature and high-yielding regioselective reactions of phenol and naphthol Mannich bases, will serve as a useful addition or even an alternative, comparable at least, to the currently available methodology.

Acknowledgment

We thank the European Social Fund (ESF) and the Operational Programme for Educational Training (EPEAEK) for funding this work through the PYTHAGORAS II programme.

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(13) **Conversion of Carbamates to Amides (Table 1); General Procedure**: *n*-BuLi (3.8 mL, 1.6 M sol in hexane) was added dropwise to a stirred solution of diisopropylamine (0.607 g, 6 mmol), in anhyd THF (6 mL) at –78 °C under a nitrogen atmosphere. After 20 min at –78 °C a solution of the appropriate carbamate (5 mmol) in anhyd THF (6 mL) was added. The reaction mixture was stirred for 30 min at –78 °C, allowed to warm to r.t., stirred for a further 6 h and then quenched with sat. NH_4Cl (5 mL). The reaction mixture was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (25 mL) and then dried (Na_2SO_4). The solvent was removed in vacuo and the crude product was purified by silica flash column chromatography (hexane–Et_2O, 6:4) to give the corresponding amide. The structures of the products were confirmed by comparison of their mp, TLC, IR or ^1H NMR data with authentic samples obtained commercially or prepared by literature methods. ***N*,*N*-Diethyl-1-hydroxy-2-naphthamide (Table 1, entry 8)**: Obtained as colourless microcrystals (EtOAc–hexane); yield: 0.87 g (72%); mp 50–52 °C; R_f 0.48 (hexane–Et_2O, 3:7). IR (KBr): 3443, 3067, 2982, 2934, 1635 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 6 H), 3.54 (q, *J* = 7.2 Hz, 4 H), 7.25–7.33 (m, 2 H), 7.45–7.58 (m, 2 H), 7.78 (d, *J* = 6.8 Hz, 1 H), 8.41 (d, *J* = 7.6 Hz, 1 H), 11.41 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 42.4, 110.6, 117.7, 123.7, 123.8, 125.7, 125.8, 127.4, 128.4, 135.6, 157.8, 172.8. ES–MS: *m*/*z* = 244.66 $[M + 1]^+$. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.78; H, 7.20; N, 5.69.

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(21) **Conversion of Amides to Mannich Bases (Table 2); General Procedure**: A solution of appropriate amide (1.25 mmol) in anhyd THF (50 mL) was added to a stirred solution of $LiAlH_4$ (0.244 g, 6.25 mmol) in anhyd THF (25 mL) at 0 °C. The reaction mixture was allowed to warm to r.t., stirred for 3 h and then treated successively with H_2O (10 mL), 15% aq NaOH (10 mL) and H_2O (40 mL). The reaction mixture was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by silica flash column chromatography eluting with Et_2O to give the corresponding Mannich base. The structure of the products was confirmed by comparison of their mp, TLC, IR or ^1H NMR data with authentic samples obtained commercially or prepared by literature methods. **2-[(Diethylamino)methyl]-1-naphthol (Table 2, entry 8)**: Obtained as a dark red oil; yield: 0.18 g (65%), mp 149–150 °C (as HCl salt); R_f 0.14 (hexane–Et_2O, 3:7). IR (KBr): 3330 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 6 H), 2.69 (q, *J* = 7.2 Hz, 4 H), 3.92 (s, 2 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 1 H), 7.41–7.49 (m, 2 H), 7.74 (m, 1 H), 8.22–8.28 (m, 1 H), 11.15 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3 (2 × C), 46.5 (2 × C), 57.2, 114.4, 118.0, 122.0, 124.7, 125.0, 125.8, 126.4, 127.3, 133.8, 154.0. ES–MS: *m*/*z* = 230.24 $[M + 1]^+$. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.25; H, 8.64; N, 5.74.

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(33) **2-[(Diethylamino)methyl]-8-(1,3-dioxolan-2-yl)-1-naphthol (8b)**: Prepared by reducing 8-(1,3-dioxolan-2-yl)-*N*,*N*-diethyl-1-hydroxy-2-naphthamide (**7b**) with $LiAlH_4$ according to the general procedure.[29] Obtained as a colourless semi-solid; yield: 42 mg (74%); R_f 0.38 (hexane–Et_2O, 1:4). IR (KBr): 3330 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 6 H), 3.50 (q, *J* = 7.2 Hz, 4 H), 3.82 (s, 2 H), 4.08–4.18 (m, 5 H), 7.27–7.90 (m, 5 H), 11.45 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.22, 41.75, 42.10, 65.09, 102.16, 114.00, 119.06, 124.16, 126.84, 129.50. ES–MS: *m*/*z* = 302.3 $[M + 1]^+$. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.48; H, 7.54; N, 4.51.

(34) **7-[(Diethylamino)methyl]-8-hydroxy-1-naphthaldehyde (9b)**: Compound **8b** (0.04 g, 0.13 mmol) was dissolved in a mixture of 10% aq HCl (10 mL) and THF (10 mL) and heated under reflux for 1 h. After cooling, 10% aq K_2CO_3

was added dropwise to the reaction mixture until pH 5, followed by extraction with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude material was purified by crystallisation from hexane–EtOAc (6:1) to give colourless microcrystals; yield: 26 g (88%); mp 128–130 °C; R_f 0.54 (hexane–Et_2O, 3:2). IR (KBr): 3335, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 6 H), 3.52 (q, *J* = 7.2 Hz, 4 H), 3.84 (s, 2 H), 7.25–8.10 (m, 5 H), 9.93 (s, 1 H), 11.85 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.39, 41.90, 117.54, 124.56, 131.59, 136.89, 192.12. ES–MS: *m*/*z* = 258.12 $[M + 1]^+$. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.49; H, 7.31; N, 5.26.

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