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Synthesis of 2-Tetralones *via* a Novel 1,2-Carbonyl Transposition of 1-Tetralones

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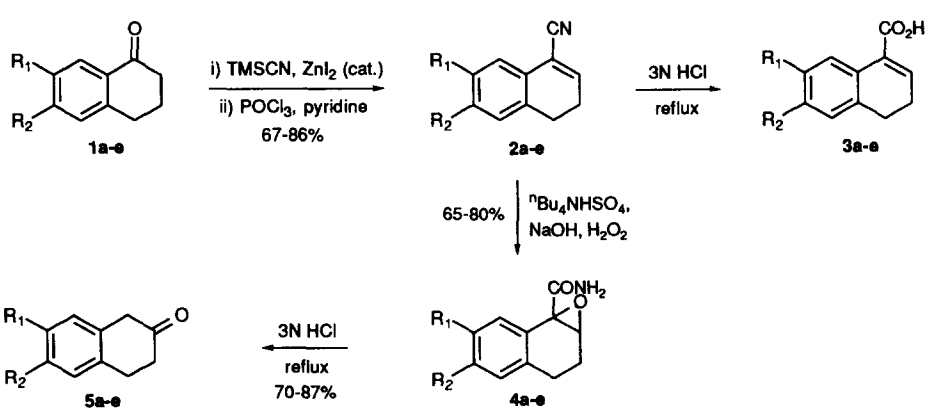
Summary: *Simple acidic hydrolysis of epoxyamides **4**, derived from 1-tetralones, furnishes the corresponding 2-tetralones in good yield.*

A number of methods exist for the 1,2-transposition of a carbonyl group in a sequence ranging from 3 to 10 steps.[1] During a study directed towards the synthesis of some tetralin-containing peptide mimics, we discovered an efficient and potentially very useful conversion of 1-tetralones to the much more difficultly accessed 2-tetralones.[2] Key intermediates in our synthetic route to these mimics were the unsaturated carboxylic acids **3**, which we expected to reach from the corresponding 1-tetralones **1**, *via* the unsaturated nitriles **2**.[3] Simple acidic hydrolysis of the latter led uneventfully to the acids **3**. However, when the hydrolysis of **2** was performed using oxidative, phase transfer conditions,[4] the epoxyamides **4** were obtained in good (65-80%) yields after only 15 min at room temperature. Surprisingly, the epoxy amides were readily transformed into the 2-tetralones **5** by heating in 3N HCl overnight.

Scheme 1



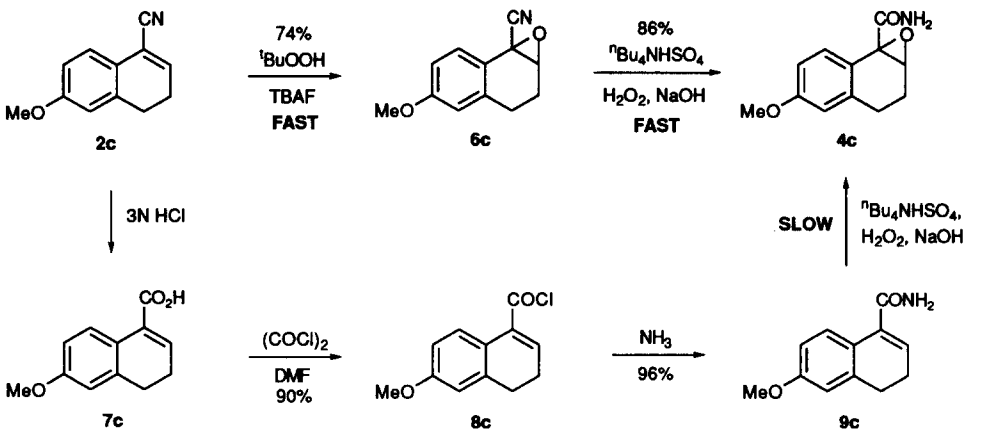
The conditions employed to hydrolyze the nitriles **2** above are not known[4] to provide epoxyamides and this product appears to be entirely peculiar to the tetralone system. When the oxidative, phase transfer hydrolysis was carried out on several other unsaturated nitriles (*e.g.* cinnamonitrile, 1-cyano-1-phenyl-but-1-ene and 1-cyano-4-methyl-cyclohexene) the expected hydrolysis to the unsaturated amide took place, and no epoxide products were observed. Furthermore, prolonged reaction times, or elevated temperatures did not yield any epoxide. The yields of the process illustrated in Scheme 1 for a series of tetralones are shown in the Table. It is seen from entry 5 that the transposition fails for 1-tetralones bearing an electron-withdrawing substituent (e.g. CO_2Me).

Table: Transposition of 1-Tetralones to 2-Tetralones.

Entry	1-Tetralone	R_1	R_2	2 (%)	4 (%)	2-Tetralone 5 (%)
1	**1a**	H	H	74	65	73
2	**1b**	OMe	H	67	80	70
3	**1c**	H	OMe	86	75	75
4	**1d**	OMe	OMe	77	68	87
5	**1e**	H	CO_2Me	35	-	-

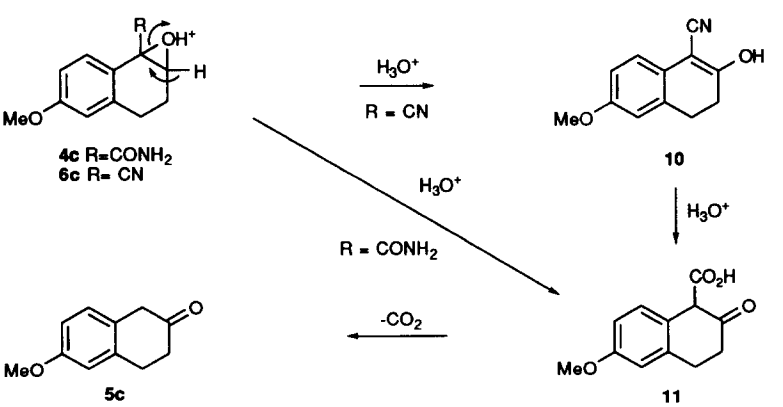
To gain some insight into why the α,β-unsaturated nitriles derived from the tetralones should yield epoxyamides, while all other systems examined did not, the experiments detailed in Scheme 2 were performed. Thus, the nitrile **2c** was epoxidised under non-hydrolysing conditions[5] and the resulting epoxynitrile **6c** subjected to the Cacchi-Misiti conditions (*n*-Bu_4NHSO_4-H_2O_2-NaOH) employed above. A rapid and complete conversion to the epoxyamide **4c** took place within 15 min at room temperature. Additionally, the nitrile, **2c**, was hydrolysed using 3N HCl to the acid **7c**, and then converted, *via* the acid chloride **8c**, to the unsaturated carboxamide **9c**. Exposure of **9c** to the Cacchi-Misiti conditions produced only a 35% yield of the epoxyamide **4c** after 6h. It is, therefore, safe to assume that epoxidation of the unsaturated nitrile **2c** occurs first followed by nitrile hydrolysis; both relatively rapid processes. For the non-tetralone-derived unsaturated nitriles examined, the rate of nitrile hydrolysis exceeds that of epoxidation, and subsequent epoxidation of the resulting unsaturated amides is uniformly slow, as seen for **9c** to **4c**.

Scheme 2



The rearrangement of the epoxyamides to the 2-tetralones appears to be without precedent. In acidic media, protonation of the epoxide in **4c**, ring opening, and proton loss, followed by hydrolysis leads to the β-keto acid **11**, which decarboxylates readily to the 2-tetralone **5c** (Scheme 3). The same product was formed from acid treatment of the epoxynitriles **6c**, although in very low (8%) yield. The major product (25%) from the epoxynitrile was the remarkably stable enol **10**. The most interesting step in the sequence requires the development of positive charge at the benzylic carbon which bears either the CN or $CONH_2$ group (**4c**, **6c**). Although somewhat unusual, it is not without precedent,[6] and explains the failure of the transposition when the aromatic ring bears an electron withdrawing substituent (i.e. CO_2Me, Table, Entry 5).[7]

Scheme 3



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References and Notes

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2. For example, the cost of 6-methoxy-1-tetralone is $1.62/g whereas that for 6-methoxy-2-tetralone is $153.50/g (Aldrich Chemical Co.).

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7. Selected physical data. **2c**) m.p. 49-50 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.44 (dt, *J* = 8.4, 4.8 Hz, 2H, C$\underline{H}_2$), 2.80 (t, *J* = 8.1 Hz, 2H, C$\underline{H}_2$), 3.80 (s, 3H, OMe), 6.75 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.5, 26.6, 55.3, 111.6, 113.8, 114.2, 117.3, 121.8, 126.1, 136.0, 140.8, 160.1; IR ($CHCl_3$ soln.) 2942, 2835, 2222, 1608 cm^{-1}; Found: C, 77.70; H, 6.07%. $C_{12}H_{11}NO$ requires C, 77.80: H, 6.00%. **4c**) m.p. 151-153 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.90-2.04 (m, 1H), 2.36-2.48 (dddd, *J* = 14.9, 6.1, 3.1, 1.3 Hz, 1H, C$\underline{H}$), 2.56-2.83 (m, 2H), 3.76 (app d, *J* ~ 1.2 Hz, 1H, C$\underline{H}$(O)), 3.80 (s, 3H, OMe), 5.54 (br s, 1H, N$\underline{H}$), 6.56-6.69 (m, 2H, N$\underline{H}$ and Ar), 6.78 (dt, *J* = 8.6, 1.2 Hz, 1H, Ar), 7.66 (dd, *J* = 8.6, 1.2 Hz, 1H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.4, 24.9, 55.2, 58.1, 62.1, 111.5, 114.4, 120.7, 130.6, 138.0, 159.8, 171.5; IR ($CHCl_3$ soln.) 3413, 3287, 1694, 1658, 1615, 1437, 1254, 747 cm^{-1}; Found: M$^+$, 219.0894. $C_{12}H_{13}NO_3$ requires M, 219.0895. **5c**) oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.50 (t, *J* = 6.9 Hz, 2H, C$\underline{H}_2$), 3.00 (t, *J* = 6.6 Hz, 2H, C$\underline{H}_2$), 3.49 (s, 2H, ArC$\underline{H}_2$CO), 3.78 (s, 3H, OMe), 6.72 (d, *J* = 2.6 Hz, 1H), 6.75 (m, 1H), 7.00 (d, *J* = 7.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 28.6, 38.1, 44.2, 55.3, 112.2, 113.2, 125.1, 129.0, 137.8, 158.4, 210.8; IR (film) 1714, 1610, 1500 cm^{-1}. **6c**) m.p. 62-64 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.81-1.96 (dt, *J* = 15.0, 5.8 Hz, 1H, C$\underline{H}_2$), 2.39-2.78 (m, 3H), 3.78 (s, 3H, OMe), 4.09 (app s, 1H, C$\underline{H}$(O)), 6.66 (s, 1H), 6.77-6.84 (m, 1H), 7.69 (d, *J* = 8.5 Hz, 1H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.5, 24.6, 48.5, 55.7, 62.0, 112.0, 115.2, 117.5, 119.3, 130.2, 137.4, 161.2; IR (film) 3004, 2940, 2246, 1614, 1580, 1318, 1139, 1038, 886 cm^{-1}; Found: M$^+$, 201.3048. $C_{12}H_{11}NO_2$ requires M, 201.0790. **10**, m.p. 160-162 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.55 (t, *J* = 6.8 Hz, 2H, C$\underline{H}_2$), 2.89 (t, *J* = 6.8 Hz, 2H, C$\underline{H}_2$), 3.79 (s, 3H, OMe), 3.75-3.87 (m, 1H), 6.71 (s, 1H, Ar), 6.72-6.77 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 1H, Ar); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 27.7, 27.9, 55.7, 86.1, 112.1, 114.4, 116.2, 122.3, 124.7, 132.4, 158.6, 168.4; IR (film) 3120, 3054, 2222, 1641, 1503; Found: M$^+$, 201.0795. $C_{12}H_{11}NO_2$ requires M, 201.0790.

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