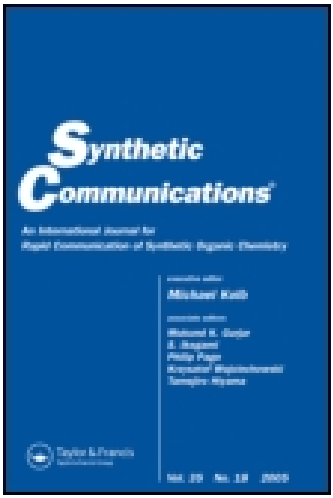

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REGIOSPECIFIC PREPARATION OF 5-ACYLAMINOTETRALONES

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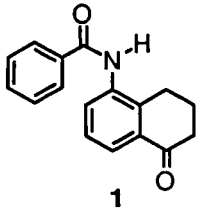
ABSTRACT: A Beckmann Rearrangement/Friedel-Crafts strategy was utilized to prepare 5-amidotetralones in high yield.

Tetralones of types **1** and **2** are useful as intermediates for the preparation of dopamine antagonists[1], antihypertensives and vasodilators[2], as well as neuromuscular blocking agents[3]. During the course of one of our projects we required quick and easy access to these tetralones. Surprisingly, a literature search provided little in the way of practical entry into these systems. Describing the [4+2] cycloaddition of nitrodienamines, Takeuchi *et al.* reported a synthesis of 5-nitro-1-



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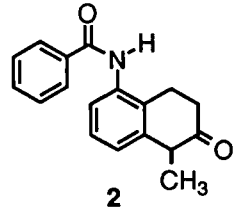

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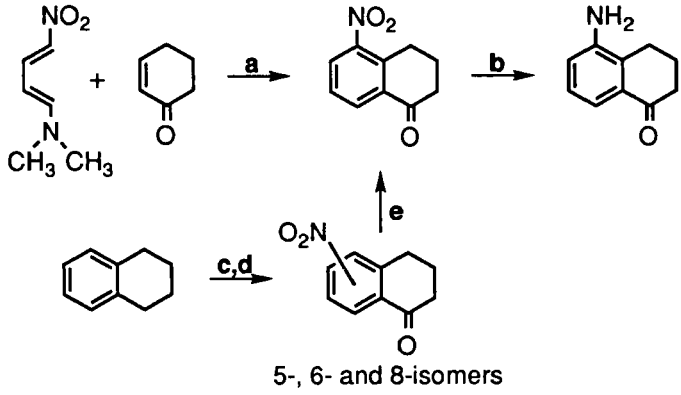
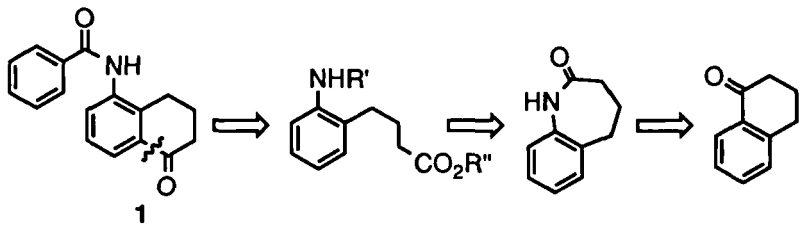
*To whom correspondence should be addressed



Scheme 1

a) xylene reflux b) $SnCl_2/FeSO_4/HCl$ c) HNO_3/H_2SO_4 d) $CrO_3/AcOH$ e) separate isomers

tetralone albeit in very low overall yield[4] (Scheme 1). The resultant aromatic nitro functionality could be reduced[3] to deliver the desired aminotetralone. Another method involved the nitration of tetralin, resulting in a mixture of 5- and 6-isomers[3,5]. Oxidation of the benzylic methylene group gave a mixture of 5-, 6- and 8-nitro-1-tetralones in low yield which were separated by fractional crystallization and chromatography. Finally, reduction of the nitro functionality afforded the desired amine. We report here the simple preparation of tetralones **1** and **2** utilizing a Beckmann Rearrangement/Friedel-Crafts strategy. Our approach, which avoids the need for tedious separation of isomers or use of special reagents, is depicted retrosynthetically in Scheme 2. The key features imparting regiospecificity in the pathway are disconnection at the carbonyl functionality of **1** to an appropriate 4-arylbutyrate and the introduction of the amino functionality via a

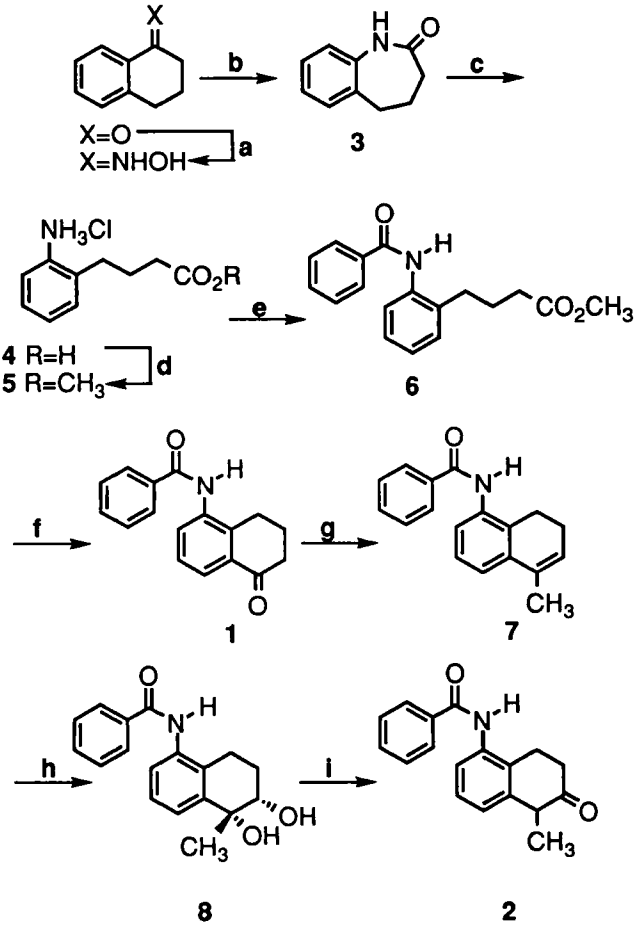


Scheme 2

lactam arising from 1-tetralone. Subsequent transformation of tetralone **1** would provide **2**.

Thus, treatment of the oxime prepared from 1-tetralone with polyphosphoric acid delivered desired rearranged product **3**[6] (Scheme 3). This lactam was hydrolyzed using hydrochloric acid and esterified in methanol to give methyl ester **5**[7]. The conversion of **3** to **5** was usually carried out in one pot without isolation of carboxylic acid **4**. Treatment with benzoyl chloride gave benzamide **6** which was subjected to an acid catalyzed cyclization. Use of polyphosphoric acid in the Friedel-Crafts reaction gave 5-benzoylamino-1-tetralone **1**, whereas sulfuric acid delivered 5-amino-1-tetralone (i.e. unprotected primary amine).

Conversion of tetralone **1** into **2** exploited 1,2-carbonyl transposition methodology[8,9]. Introduction of the alkyl substituent found in **2** was easily accomplished by treating tetralone **1** with methylmagnesium bromide. The intermediate tertiary alcohol from this Grignard reaction, which could be isolated if desired, was dehydrated under the acidic conditions of work-up to deliver olefin **7** directly. Although transformation of olefin **7** into tetralone **2** via rearrangement of a m-chloroperbenzoic acid-derived epoxide was initially investigated, its



Scheme 3

a) $NH_2OH{\cdot}HCl/CH_3OH/NaOH$ (90%) b) PPA (93%) c) HCl/H_2O (97%)
d) HCl/CH_3OH (98%) e) $PhCOCl/Et_3N/CH_3CN$ (97%) f) PPA (74%)
g) CH_3MgBr/THF, HCl/H_2O (87%) h) cat.OsO_4/NMO/acetone/H_2O (95%)
i) p-TSA/toluene (98%)

rearrangement to **2**, catalyzed by various acids (e.g. p-Tsa, HCl, $BF_3 \cdot Et_2O$) resulted in complex mixtures. Consequently, osmium tetroxide-catalyzed dihydroxylation to diol **8** followed by acid catalyzed dehydration cleanly gave the desired 5-benzoylamino-1-methyl-2-tetralone **2**.

In conclusion, a simple regiospecific high yielding approach was developed for the preparation of 5-acylaminotetralones **1** and **2** from inexpensive and readily available starting materials.

EXPERIMENTAL

1-Tetralone Oxime.

To a solution of 200.0 g (1.37 mol) of 1-tetralone and 142.0 g (2.05 mol) of hydroxylamine hydrochloride in 600 mL of methanol was added 164.0 g (2.05 mol) of 50% aqueous sodium hydroxide. The reaction was refluxed for 2h, concentrated *in vacuo*, diluted with 2.5 L of water and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The resulting solid was recrystallized from 2-propanol to deliver 197.6 g (1.23 mol) of desired oxime, mp 98-100^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 1.75(m,2H), 2.70(m,4H), 7.20(m,3H), 7.83(m,1H), 11.05(s,1H). Anal. Calc. for $C_{10}H_{11}NO$: C 74.51, H 6.88, N 8.69. Found: C 74.45, H 6.87, N 8.67.

2,3,4,5-Tetrahydro-1H-benzazepin-2-one (*3*).

A 1 L three-necked flask equipped with a mechanical stirrer and nitrogen flow was charged with 100 g of polyphosphoric acid and heated to 125^{0}C. 1-Tetralone oxime, 15.0 g (93.2 mmol), was added in

one portion and stirred for 5 minutes. The reaction mixture was poured over ice and extracted with dichloromethane. The organic layer was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization from ethyl acetate/cyclohexane yielded 14.0 g (87.0 mmol) of lactam **3** as a white powder, mp 134-9^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 2.10(m,4H), 2.68(m,2H), 6.95-7.25(m,4H), 9.46(s,1H). Anal. Calc. for $C_{10}H_{11}NO$: C 74.51, H 6.88, N 8.69. Found: C 74.45, H 6.85, N 8.75.

4-(2-Aminophenyl)butyric acid hydrochloride **(4).**

A mixture of 100.0 g (0.621 mol) of lactam **3** in 600 mL of concentrated hydrochloric acid was heated to reflux for 2h. After cooling in an ice bath the white solid was collected by filtration and dried ($MgSO_4$) *in vacuo* to give 130.1 g (0.602 mol) of the hydrochloride salt mp, 216-9^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 1.81(m,2H), 2.25(t,2H), 2.65(t,2H), 7.35(m,4H), 10.16(br s,4H). Anal. Calc. for $C_{10}H_{14}ClNO_2$: C 55.69, H 6.54, N 6.50. Found: C 55.67, H 6.40, N 6.40.

Methyl 4-(2-aminophenyl)butyrate hydrochloride **(5).**

A solution of 216.2 g (1.0 mol) of carboxylic acid **4** in 600 mL of methanolic hydrogen chloride was refluxed for 4h. Concentration *in vacuo* followed by recrystallization from ethyl acetate delivered 244.0 g (0.978 mol) of the hydrochloride salt as a hydrate, mp 72-5^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 1.81(m,2H), 2.39(t,2H), 2.73(t,2H), 3.60(s,3H), 7.35(m,4H), 10.16(br s,4H). Anal. Calc. for $C_{11}H_{16}ClNO_2 \cdot 1.1H_2O$: C 52.98, H 7.35, N 5.62. Found: C 53.10, H 7.12, N 5.59.

Methyl 4-(2-benzoylaminophenyl)butyrate (6).

A three-necked 2 L flask equipped with a mechanical stirrer and nitrogen flow was charged with 600 mL of acetonitrile followed by 89.0 g (0.359 mol) of ester **5** and 86.0 g (0.851 mol) of triethylamine. To this mixture was added 59.6 g (0.425 mol) of benzoyl chloride and a catalytic amount of 4-dimethylaminopyridine. After stirring at ambient temperature for 3h, the reaction was concentrated *in vacuo*, diluted with 10% aqueous hydrogen chloride and extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization from ethyl acetate/cyclohexane delivered 103.1 g (0.347 mol) of the desired amide, mp 83-5^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 1.78(m,2H), 2.25(t,2H), 2.65(t,2H), 3.48(s,3H), 7.25(m,4H), 7.58(m,3H), 7.99(m,2H), 9.90(s,1H). Anal. Calc. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71. Found: C 72.67, H 6.38, N 4.70.

5-Benzoylamino-1-tetralone (1).

A three-necked 2 L flask equipped with a mechanical stirrer and nitrogen flow was charged with 1200 g of polyphosphoric acid and heated to 120^{0}C. Amide-ester **6**, 100.0 g (0.337 mol), was added in one portion. After heating for 1h the mixture was poured over ice and extracted with dichloromethane. The organic layer was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization from acetone/cyclohexane yielded 66.0 g (0.249 mol) of the desired tetralone, mp 167-9^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 2.01(m,2H), 2.61(t,2H), 2.86(t,2H), 7.40-8.10(m,9H). Anal. Calc. for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28. Found: C 76.78, H 5.67, N 5.18.

5-Benzoylamino-1-methyl-3,4-dihydronaphthalene **(7).**

A three-necked 1 L flask equipped with a mechanical stirrer and nitrogen flow was charged with 140 mL (0.419 mol) of a 3.0M methylmagnesium bromide solution. To this stirring mixture was added 37.0 g (0.140 mol) of tetralone **1** in 500 mL of tetrahydrofuran over 15 minutes at ambient temperature. After stirring an additional 4h the reaction was quenched with 10% aqueous hydrogen chloride. The reaction mixture was stirred for 1h and extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography using silica gel (1% methanol/dichloromethane as eluant) gave 32.1 g (0.122 mol) of desired olefin **7**, mp 161-3^{0}C and 4.0 g (0.015 mol) of recovered starting material **1**. ^{1}H NMR (δ) ($CDCl_3$): 2.01(s,3H), 2.26(m,2H), 2.73(m,2H), 5.88(m,1H), 7.18-7.90(m,9H). Anal. Calc. for $C_{18}H_{17}NO$: C 82.10, H 6.51, N 5.32. Found: C 81.82, H 6.49, N 5.21.

5-Benzoylamino-1,2-dihydroxy-1-methyl-1,2,3,4-tetrahydronaphthalene ***(8).***

To a solution of 10.0 g (38.0 mmol) of olefin **7** in 200 mL of acetone and 50 mL of water was added 11.1 g (95.1 mmol) of 4-methylmorpholine N-oxide. A catalytic amount of osmium tetroxide was added and the reaction stirred for 24h at ambient temperature. After addition of 200 g of silica gel the reaction was concentrated *in vacuo*. Toluene was used to azeotropically remove most of the remaining water *in vacuo*. The solid was poured on to an additional amount of silica gel in a glass column and eluted with ethyl acetate and finally 50% methanol/ethyl acetate. Concentration of the appropriate fractions *in vacuo* delivered

10.7 g (36.0 mmol) of a white solid, mp 201-3^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 1.39(s,3H), 1.86(m,2H), 2.60(m,1H), 2.80(m,1H), 2.64(m,1H), 4.49(s,1H) 4.63(m,1H), 7.20(m,2H), 7.55(m,4H), 7.99(m,2H), 9.69(s,1H). Anal. Calc. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71. Found: C 72.46, H 6.56, N 4.57.

5-Benzoylamino-1-methyl-2-tetralone (2).

A solution of 6.0 g (20.2 mmol) of diol **8** and 0.5 g (2.6 mmol) of p-toluenesulfonic acid in 150 mL of toluene was heated to reflux for 5 minutes. The reaction was poured into aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization from toluene yielded 5.5 g (19.7 mmol) of a white solid, mp 181-4^{0}C. ^{1}H NMR (δ) (d_6-DMSO): 1.39(d,3H), 2.30(m,1H), 2.55(m,2H), 2.99(m,2H), 3.69(q,1H), 7.15(m,1H), 7.23(m,2H), 7.68(m,3H), 8.00(m,2H), 10.13(s,1H). Anal. Calc. for $C_{18}H_{17}NO_2$: C 77.40, H 6.13, N 5.01. Found: C 77.46, H 6.06, N 4.90.

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