Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Short, Efficient Synthesis of 6-Cyano-1-tetralones

Carmen Almansa [a], Elena Carceller [a], Javier Bartrolí [a] & Javier Forn [a]
[a] Chemistry Laboratories, Research Center, J. Uriach & Cía.S.A., Degà Bahí 59-67, 08026, Barcelona, Spain
Published online: 23 Sep 2006.

To cite this article: Carmen Almansa, Elena Carceller, Javier Bartrolí & Javier Forn (1993) A Short, Efficient Synthesis of 6-Cyano-1-tetralones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:21, 2965-2971, DOI: 10.1080/00397919308011138

To link to this article: http://dx.doi.org/10.1080/00397919308011138

SYNTHETIC COMMUNICATIONS, 23(21), 2965-2971 (1993)

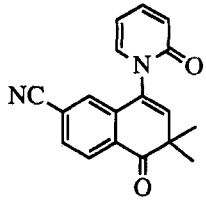
A SHORT, EFFICIENT SYNTHESIS OF 6-CYANO-1-TETRALONES.

Carmen Almansa, Elena Carceller, Javier Bartrolí, and Javier Forn* .

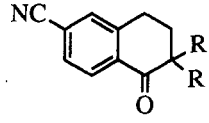
Chemistry Laboratories, Research Center, J. Uriach & Cía.S.A., Degà Bahí 59-67, 08026 Barcelona, Spain.

Abstract: A new, short and high-yield synthesis of 6-cyano-1-tetralones is described. Triflate intermediates **8** and **9** are versatile intermediates for the synthesis of other 6-substituted tetralones.

Work from these laboratories has led to the identification of UR-8225 (**1**)[1], a potent potassium channel activator which has been selected for clinical trials. The synthesis of large amounts of this compound required an efficient procedure for the preparation of 2,2-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-6-carbonitrile **3**, which is easily transformed into **1** in three steps[1a].



1 (UR-8225)



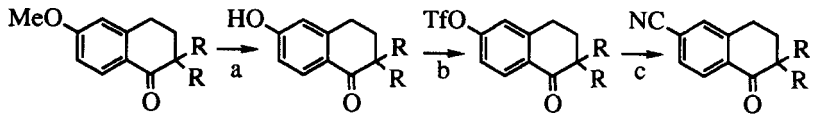
2 R = H
3 R = Me

* To whom correspondence should be addressed.

Compound **3** was initially obtained by methylation of the known 1-oxo-1,2,3,4-tetrahydronaphthalen-6-carbonitrile (6-cyano-1-tetralone) **2**. Although it has been used as starting material for the preparation of several pharmaceutical compounds[2], the only published procedure[3] for obtaining **2** gives a 17% overall yield and requires a six step sequence, which involves acylation of 1,2,3,4-tetrahydronaphthalen-1-one[4] followed by oxime formation and Beckmann rearrangement[5], regioselective benzylic oxidation at the amide *para*-position, amide hydrolysis and final conversion of the resultant amino group into a carbonitrile under Sandmeyer conditions.

Use of Stille's aryl triflate methodology[6] was envisaged as a suitable alternative to this lengthy procedure. Cyanation of aromatic triflates had been previously described[7] and commercially available 6-methoxy-1-tetralone was an attractive starting product for the preparation of 6-trifluoromethanesulfonyl-1-tetralone.

Either 6-methoxy-1-tetralone **4** or its dimethyl analogue **5**[1a] were converted into fenol derivatives **6**[8] and **7**[1a], respectively, upon treatment with 48% aqueous hydrobromic acid (Scheme I). Reaction of **6** and **7** with trifluoromethanesulfonic anhydride in pyridine provided good yields of triflates **8** and **9**, respectively. Conversion of triflate **9** into carbonitrile **3** was initially tried using standard conditions for cyanation of aromatic halides (CuCN/NMP)[9], but without success. We then turned to the nickel-catalyzed process[7] and indeed, treatment of **8** or **9** with potassium cyanide in the presence of tetrakistriphenylphosphinenickel(0) generated *in situ* from bistriphenylphosphine-nickel(II) bromide and Zn/PPh_3, afforded carbonitriles **2** and **3** with excellent yields. We later found that this reaction could be performed with comparable



4 R = H **6** R = H **8** R = H **2** R = H
5 R = Me **7** R = Me **9** R = Me **3** R = Me

a: 48% HBr, reflux, 3h; b: $(TfO)_2O$, pyridine, room temperature, 18 h; c: NaCN, $Ni(PPh_3)_2Br_2$ or $Ni(PPh_3)_2Cl_2$, Zn, PPh_3, CH_3CN, 60 °C, 3 h.

Scheme I

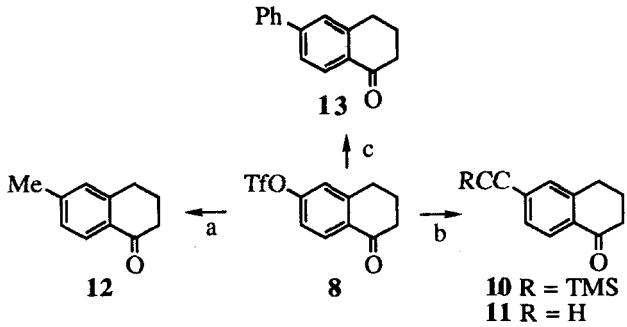
yields employing the cheaper compound bistriphenylphosphine-nickel(II) chloride.

This three step sequence substantially improves the published procedure for obtaining **2** in respect to both length and overall yield (77% compared to 17%). A similar result is observed in the large scale synthesis of the dimethyl analogue **3** (69% overall yield).

Triflates **8** and **9** are also useful intermediates for the synthesis of other 6-substituted tetralones. While the synthesis of 7-substituted tetralones from the corresponding aromatic derivatives and succinic anhydride is well established[10], there is no generally used method of synthesis for the 6-isomers, all methods being more or less laborious[11]. Since aryl triflates undergo regioselective substitution with a wide range of nucleophiles[6,12], compounds **8** and **9** represent an easy entry to the general synthesis of 6-substituted tetralones. As an example of the versatility of these compounds, we have prepared ethynyl (**11**), methyl (**12**) and phenyl (**13**) derivatives from triflate **8** using published procedures[6,12].

EXPERIMENTAL

2,2-Dimethyl-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one, 7. A mixture of **5** (346 g, 1.7 mol) and 48% HBr (3.14 L) was heated to reflux



a: $SnMe_4$, $Pd(PPh_3)_2Cl_2$, DMF, 90 °C, 18 h; b: i) TMSCCH, $Pd(PPh_3)_2Cl_2$, NEt_3, DMF, 90 °C, 2 h; ii) K_2CO_3, MeOH, room temperature, 1.5 h; c: $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, H_2O, 80 °C, 18h.

Scheme II

for 3 h followed by distillation to half of the initial volume. The mixture was poured into H_2O and extracted with Et_2O. The organic phase was extracted with 1N NaOH. The aqueous phase was acidified with 1N HCl and the precipitate was filtered and dried over P_2O_5, to afford **7**[1a] as a brown solid, which was recrystallized from EtOAc (290.3 g, 90%): mp 141°C.

6-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-one, 6. Using the same procedure described for **7** but starting from **4** (3.00 g), **6** was obtained as a brown solid (2.76 g, 99%): mp 148-152 °C (described[8] 150 °C).

2,2-Dimethyl-1,2,3,4-tetrahydro-6-trifluoromethanesulfonyl-oxynaphthalen-1-one, 9. To a solution of **7** (143.6 g, 0.75 mol) in pyridine (417 mL) at 0 °C was added dropwise under an argon atmosphere, trifluoromethanesulfonic anhydride (250 g, 0.88 mol) and the mixture was stirred at room temperature for 18 h. The mixture was poured into H_2O and extracted with Et_2O. The organic phase was washed with 1N HCl and dried over $MgSO_4$. The solvent was removed and the residue (250 g) was distilled to give **9** as a colorless oil which solidified upon standing (219.07 g, 90%): bp 150-155 °C (0.05 mmHg); mp 29-31 °C; IR (KBr) ν 2956, 2923, 1683, 1600, 1420, 1216, 1139, 1121, 1067, 938 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.12 (d, J= 8.6Hz, 1H, Ar), 7.23 (m, 2H, Ar), 3.03 (t, J= 6.4Hz, 2H, CH_2Ar), 2.01 (t, J= 6.4Hz, 2H, CH_2), 1.23 (s, 6H, $2CH_3$). Anal. ($C_{13}H_{13}F_3SO_4$) C, H.

1,2,3,4-Tetrahydro-6-trifluoromethanesulfonyloxynaphthalen-1-one, 8. Using the same procedure described for **9** but starting from **6** (1.00 g), **8** was obtained as a colorless oil (1.44 g, 80%): bp 170-175 °C (0.5 mmHg); IR (KBr) ν 2945, 1683, 1420, 1212, 1138, 942, 894 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.13 (d, J= 8.6Hz, 1H, Ar), 7.24 (m, 2H, Ar), 3.02 (t, J= 6.4Hz, 2H, CH_2Ar), 2.69 (t, J= 6.4Hz, 2H, CH_2), 2.24 (m, 2H, CH_2). Anal. ($C_{11}H_9F_3SO_4$) C, H.

2,2-Dimethyl-1,2,3,4-tetrahydro-1-oxonaphthalen-6-carbonitrile, 3. A suspension of **9** (208.07 g, 0.65 mol), bistriphenyphosphinenickel(II) bromide (24.52 g, 0.033 mol), triphenylphosphine (17.89 g, 0.067 mol), Zn powder (12.90 g, 0.20 mol), KCN (46.61 g, 0.71 mol) and acetonitrile (590 mL) was stirred at 60 °C under an argon atmosphere for 3 h. After cooling, the mixture was poured into H_2O and extracted with Et_2O and EtOAc. The organic phase was filtered through celite, and dried over $MgSO_4$. The solvent was removed and the residue was recrystallized from EtOAc-hexane (500:50) to give 99.4 g of **3** as an off-white solid. The mother liquors were purified by flash chromatography (hexane-EtOAc), to afford an additional 9.8 g of product (combined yield 85%): mp 142-144 °C; IR (KBr) ν 2979, 2958, 2917, 2225, 1672, 1600, 1446, 1377, 1301, 1220, 967 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.12 (d, J= 8.6Hz, 1H, Ar), 7.58 (m, 2H, Ar), 3.02 (t, J= 6.4Hz, 2H, CH_2Ar), 2.01 (t, J= 6.4Hz, 2H, CH_2), 1.23 (s, 6H, $2CH_3$). Anal. ($C_{13}H_{13}NO$) C, H, N.

Starting from 1 g of **9** and using bistriphenyphosphinenickel(II) chloride instead of bistriphenyphosphinenickel(II) bromide, 85% yield of **3** was obtained.

1,2,3,4-Tetrahydro-1-oxonaphthalen-6-carbonitrile, 2. Using the same procedure described for **3** but starting from **8** (0.30 g), **2** was obtained as a yellow solid, which was recrystallized from CH_2Cl_2 (0.18 g, 97%): mp 134-135 °C (described from aqueous ethanol[3]: 133-134 °C).

1,2,3,4-Tetrahydro-6-trimethylsilylethynylnaphthalen-1-one, 10. A solution of **8** (0.50 g, 1.7 mmol), trimethylsilylacetylene (0.34 mL, 2.4 mmol), triethylamine (1 mL, 7.0 mmol), bistriphenyphosphinepalladium(II) chloride (0.034 g, 0.048 mmol), and dimethylformamide (5 mL) was stirred at 90 °C under an argon atmosphere for 2 h. After cooling, the mixture was poured into H_2O and extracted with Et_2O. The organic phase was washed with H_2O and dried over $MgSO_4$. The solvent was removed to afford **10** as an oil (0.30 g, 73%): IR

(KBr) ν 2949, 2150, 1679, 1597, 1274, 1246 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.95 (d, J= 8.6Hz, 1H, Ar), 7.40 (m, 2H, Ar), 2.92 (t, J= 6.4Hz, 2H, CH_2Ar), 2.65 (t, J= 6.4Hz, 2H, CH_2), 2.18 (m, 2H, CH_2), 0.25 (s, 9H, $SiMe_3$).

6-Ethynyl-1,2,3,4-tetrahydronaphthalen-1-one, 11. A solution of **10** (0.30 g, 1.2 mmol), K_2CO_3 (0.016 g, 0.1 mmol) and MeOH (3 mL) was stirred at room temperature for 1.5 h. The solvent was removed and the residue dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$ and the solvent was removed, to afford **11** as an oil (0.23 g, 100%): IR (KBr) ν 3278, 3242, 2930, 2097, 1672, 1597, 1401, 1320, 1276, 1227, 1183 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.98 (d, J= 8.6Hz, 1H, Ar), 7.44 (m, 2H, Ar), 3.21 (s, 1H, CH), 2.94 (t, J= 6.4Hz, 2H, CH_2Ar), 2.66 (t, J= 6.4Hz, 2H, CH_2), 2.12 (m, 2H, CH_2).

6-Methyl-1,2,3,4-tetrahydronaphthalen-1-one, 12. A solution of **8** (0.50 g, 1.7 mmol), $SnMe_4$ (0.314 g, 1.7 mmol), LiCl (0.216 g, 5.1 mmol), $Pd(PPh_3)_2Cl_2$ (0.024 g, 0.034 mmol), a crystal of 2,6-di-tert-butyl-4-methylfenol and DMF (7 mL) was stirred under nitrogen at 90 °C for 18 h. The mixture was poured into water and extracted with Et_2O. The organic phase was washed with saturated NH_4Cl and dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (hexane-EtOAc) to afford **12** as an oil (0.2 g, 74%): bp 113 °C (2.5 mmHg)[12a].

6-Phenyl-1,2,3,4-tetrahydronaphthalen-1-one, 13. A solution of **8** (0.20 g, 0.7 mmol), $Pd(PPh_3)_4$ (0.023 g, 0.02 mmol), Na_2CO_3 (0.144 g, 1.4 mmol), $PhB(OH)_2$ (0.083 g, 0.7 mmol), toluene (2.4 mL) and H_2O (0.7 mL) was stirred under nitrogen at 80 °C for 18 h. The mixture was poured into water and extracted with Et_2O. The organic phase was washed with H_2O and dried over $MgSO_4$. The solvent was removed, to afford **13** as a white solid which was recrystallized from Et_2O (0.120 g, 79%): mp 112.3-122.8°C (described[13] 106-108°C).

Acknowledgment. This work was done with support of the "Plan de Fomento de la Investigación en la Industria Farmacéutica", from the "Ministerio de Industria y Energía (Exp. 656/91)". We thank M. Carmen Torres, Concepción González, Consol Ferreri and Guadalupe Martínez for their excellent technical assistance.

REFERENCES

1. a) Almansa, C.; Gómez, L. A.; Cavalcanti, F. L.; Rodríguez, R.; Carceller, E.; Bartrolí, J.; García-Rafanell, J. and Forn, J. *J. Med. Chem.* Accepted for publication; b) Casis, O.; Pérez-Vizcaino, F.; Rodríguez, R.; Cavalcanti, F. L.; Gómez, L. A.; García-Rafanell, J.; Tamargo, J. *Br. J. Pharmacol.*, **1993**, *108*, 182P.
2. See i.e.: a) Vechietti, V.; Giordani, A. European Patent Application EP 333315; b) Itoh, K.; Miyake, A.; Tada, N.; Hirata, M.; Oka, Y. *Chem. Pharm. Bull*, **1984**, *32*, 130.
3. Allinger, N. L.; Jones, E. J. *J. Org. Chem.*, **1962**, *27*, 70.
4. Newman, M. J.; Zahn, H. V. *J. Am. Chem. Soc.*, **1943**, *65*, 1097.
5. Shofield, K.; Swain, T.; Theobald, A. J. *J. Chem. Soc.*, **1949**, 2399.
6. Echevarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.*, **1987**, *109* , 5478.
7. Chambers, M. R. I.; Widdowson, D. A. *J. Chem. Soc. Perkin Trans. I*, **1989**, 1365.
8. Haberland, G. *Chem. Ber.*, **1936**, *69*, 1380. The obtention of **6** from 6-methoxytetralone and HBr/AcOH, with 55 % yield is described.
9. Ellis, G. P.; Rommey-Alexander, T. M. *Chem. Rev.*, **1987**, *87*, 779.
10. Griffin, R. W.; Gass, J. D.; Berwick, M. A.; Shulman, R. S. *J. Org. Chem.*, **1964**, *29*, 2109.
11. a) 6-Me: All published procedures involve more than 4 steps with overall yields below 30%, i.e.: Bonnier, J. M.; Rinardo, J. *Bull. Soc. Chim. Fr.*, **1970**, 146; b) 6-Et: 3 steps, but involves difficult separation of 6 and 7-isomers: Horii, Z. I.; Yamamura, S.; Hakusui, H.; Nishikado, T.; Momose, T. *Chem. Pharm. Bull.*, **1968**, *16*, 2456; c) Pr^i: Stork, G.; Shulenberg, J. W. *J. Am. Chem. Soc.*, **1962**, *84*, 284.
12. a) Silanes: Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.*, **1991**, *113*, 7075; b) Boranes: Oh-e, T.; Miyaura, N.; Suzuki, A. *Chem. Lett.*, **1990**, 221; c) Grignard reagents: Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.*, **1992**, *57*, 4066; d) Boric acids: Fu, J.; Snieckus, V. *Tetrahedron Lett.*, **1990**, 1665; e) Preparation of acetylenes: Chen, Q.; Yang, Z. *Tetrahedron Lett.*, **1986**, 1171.
13. El-Zohry, M. F.; El-Khawaga, A. M. *J. Org. Chem.*, **1990**, *55*, 4036.

(Received in the UK 03 June 1993)