Pergamon

Tetrahedron Letters, Vol. 36, No. 38, pp. 6815-6818, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01403-9

General Preparation of 3-Alkyl-1-Naphthols[1]

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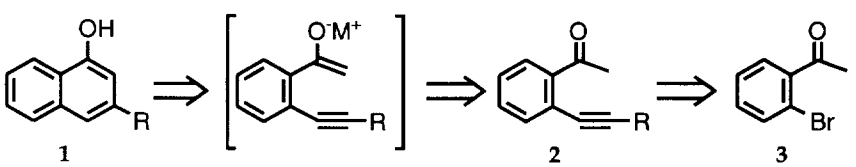
Key words: Cycloaromatization, enynone, ynenone, 3-alkyl-1-naphthol.

Abstract: *Potassium enolates derived from readily available o-alkynylacetophenones undergo intramolecular cycloaromatization on heating to afford 3-alkyl-1-naphthols in good yields.*

As part of a program directed towards inhibitors of arachidonic acid metabolism a variety of 3-alkyl-1-naphthols **1** were required as synthetic intermediates. A general, but rather lengthy, route to this series has been reported by Kasturi *et. al.*[2] More concise approaches were also known in the literature but required photochemical steps[3] or exotic cyclobutenone reagents[4] not readily amenable to scale-up. Recent examples of preparatively useful enynone cyclo-aromatizations[5] suggested the novel retrosynthetic disconnection to the benzo*ynenone* **2** depicted in Scheme 1.



1 **2** **3**

Scheme 1

Heck coupling[6] of *o*-bromoacetophenone **3** with propyne **4a** (R = Me) provided *o*-propynylacetophenone **2a** in 72% yield. Deprotonation of this ketone with potassium hexamethyldisilazide (KHMDS, 1.1 eq.) in toluene (or THF) at -78°C followed by heating at 75°C for one hour effected cycloaromatization[7] to afford 3-methyl-1-naphthol **1a** in 74% yield, following acidic work-up and distillation. All spectral and physical properties for this material were in accord with reported literature values.[3]

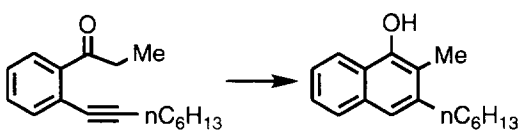
A variety of other 3-alkyl-1-naphthols were prepared similarly by this facile two-step process (Table 1). Base-mediated cycloaromatization proceeded in good yield for all substrates derived from alkylacetylenes.[8] Only the phenylacetylene derivative **2g** failed to cyclize under the standard conditions; it gave multiple products on forcing.

Table 1. Preparation of 3-Alkyl-1-naphthols.

	Alkyne **4** R-C≡CH, R =	Heck coupling % Yield **2**	KHMDS Cyclization % Yield **1**	mp **1**, °C	Analysis **1**
a	Me	72[a]	74	94-95[b]	For: $C_{11}H_{10}O$ Calcd: C 83.52; H 6.37 Fnd: C 83.64; H 6.32
b	*n*-hexyl	61	74	38-39	For: $C_{16}H_{20}O$ Calcd: C 84.16; H 8.83 Fnd: C 84.47; H 8.71
c	*c*-hexyl	73	92	99-101	For: $C_{16}H_{18}O$ Calcd: C 84.91; H 8.02 Fnd: C 85.38; H 8.01
d	*t*-butyl	63	75[c]	82-83[d]	For: $C_{14}H_{16}O$ Calcd: C 83.96; H 8.05 Fnd: C 83.98; H 8.05
e	benzyl	20	95	oil	For: $C_{17}H_{14}O$ Calcd: C 87.15; H 6.02 Fnd: C 86.74; H 6.07
f	*i*-butyl	75	70	35-36	For: $C_{14}H_{16}O$ Calcd: C 83.96; H 8.05 Fnd: C 83.90; H 8.15
g	phenyl	75	~0	n/a	n/a

a) Reaction under 1 atm propyne (xs). b) Lit. 92-93°C.[3] c) Toluene, 110°C, 21 h. d) Lit. 80-81°C, spectra as cited.[4d]

This general process is also amenable to the preparation of 2,3-dialkyl-1-naphthols. *o*-Octynylpropiophenone **5** was cyclized with KHMDS to afford 2-methyl-3-hexyl-1-naphthol **6** in 70% yield.[9]

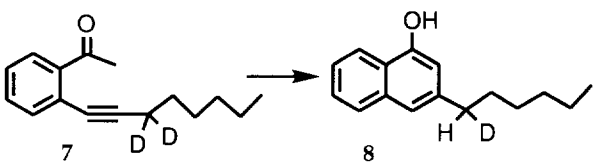


5 **6**

The cycloaromatization reaction is mechanistically intriguing. A potassium counterion appears to be required: potassium *t*-butoxide or potassium hydride in THF also promote the cyclization, but NaHMDS, LiHMDS and LDA fail in our hands.[10] Also, attempted thermal cyclization of the trimethylsilylenol ether[11] derived from **2b** gave multiple products.

A mechanism involving acetylene→allene isomerization, followed by rapid allenyldiene

6π-electrocyclization, has been proposed for related acid-catalyzed cyclizations.[5b,d] To test for an analogous mechanism under basic conditions, the dideuterated compound **7** (>98% 3,3-d_2) was prepared.[12] Cycloaromatization (0.95 KHMDS, tol, 80°C, 2h) afforded naphthol **8** with ~80% monodeuteration at the benzylic position (^{1}H NMR δ 2.66, 1H, tt, J = 7.9, 1.9 [H-D]), consistent



7 8

with an intermediate allene. However, successful cyclization of the *t*-butylacetylene derivative **2d**, which cannot isomerize, demonstrates that under somewhat more strenuous conditions (1.1 KHMDS, tol, 110°C, 21 h) there is also a mechanistic path available involving direct attack of the enolate on the alkyne triple bond.

Acknowledgement. The authors thank Dr. Keith A. M. Walker for helpful discussions.

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6. *General procedure for Heck coupling* (Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146): ***o*-Octynylacetophenone 2b**. A solution of *o*-bromoacetophenone **3** (1.99 g, 10 mmol), 1-octyne **4b** (2.20 g, 20 mmol), dimethylformamide (20 mL) and triethylamine (10 mL) was degassed by three cycles of evacuation and filling under argon. Copper (I) iodide (57 mg, 0.3 mmol) and bis(triphenylphosphine)palladium(II) chloride (280 mg, 0.4 mmol) were added and the mixture was heated at reflux for 1 h. The resulting dark orange mixture was cooled, poured into ice-cold 2M H_2SO_4 (150 mL) and extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed with water (100 mL) dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel (EtOAc : hexane, 1 : 9) to afford **2b** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, ddd, *J* = 0.2, 1.3, 7.7 Hz), 7.31 (1H, ddd, *J* = 1.3, 7.7, 7.6 Hz), 7.39 (1H, ddd, *J* = 1.3, 7.6, 7.6 Hz), 7.49 (1H, ddd, *J* = 0.2, 1.3, 7.6 Hz), 2.45 (2H, t, *J* = 7.0 Hz), 1.62 (2H, q, *J* = 7.1), 1.45 (2H, m 1.33 (4H, m), 0.90 (3H, t, *J* = 6.9 Hz), 2.45 (3H, s). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 201.0 (s), 141.1 (s), 133.9 (d), 131.0 (d), 128.2 (d), 127.5 (d), 122.5 (s), 96.9 (s), 79.6 (s), 31.3 (t), 30.0(t), 28.6 (t), 28.4 (t), 22.5(q), 19.7 (t), 14.0 (q). Mass spectrum *m/z*(%): 228 (M^+, 32): 213 (4); 199 (10); 185 (12); 171 (92); 158 (98).
7. *General procedure for cycloaromatization:* ***3-n*-Hexyl-1-naphthol 1b**. A solution of *o*-octynylacetophenone **2b** (684 mg, 3 mmol) in toluene (3 mL) was added dropwise over 10 min to a slurry of KHMDS in toluene (0.5 M, 7.2 mL, 3.6 mmol) at -78°C under argon. The resulting yellow

solution was heated to 80°C, whereupon it rapidly darkened. After 1 h, the thick red-brown mixture was cooled, acidified with 1M H_2SO_4 (20 mL) and extracted with Et_2O (2 x 20 mL). The extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (EtOAc : hexane, 1 : 9) to afford **1b** as an off-white solid: IR (KBr): 3650-3200 (w,br), 2930, 1310, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (1H, d, J = 1.6 Hz), 7.24 (1H, bs), 7.75 (1H, dd, J = 8.3, 1.3 Hz), 7.43 (1H, m), 7.47 (1H, m), 8.12 (1H, dd, J =8.0, 1.4 Hz), 2.70 (2H, t, J = 7.7 Hz), 1.69 (2H, q, J = 7.2 Hz), 1.34 (6H, m), 0.91 (3H, t, J = 6.9 Hz), 5.30 (1H, s, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 151.2 (s), 141.0 (s), 135.9 (s)127.2 (d), 126.4 (d), 124.4 (d), 122.9 (s), 121.4 (d), 119.2 (d), 110.2 (d), 36.1 (t), 31.8 (t), 31.2 (t), 29.0 (t), 22.6 (t), 14.1 (q). Mass spectrum *m/z* (%): 228 (M^+, 24); 171 (12); 158 (98); 128 (21).

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9. *o*-Octynylpropiophenone **5** was prepared from *o*-bromobenzaldehyde in 30% overall yield (unoptimized) by: i) Heck coupling with **4b** (see note 6); ii) alkylation with ethylmagnesium bromide (2 eq., THF, -78°C, 10 min.) iii) oxidation with Dess-Martin reagent (1.5 eq., CH_2Cl_2, 23°C, 15 min. [Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155]).
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12. Alkyne for Heck coupling was prepared in 30% overall yield (unoptimized) from hexanoyl chloride by: i) reduction with $LiAlD_4$ (1 eq., >99% *d* , Et_2O, 0°C, 1 h); ii) bromination with phosphorous tribromide (0.4 eq., hexane, reflux, 24 h); iii) alkylation with lithium acetylide•EDA complex (1.2 eq., DMSO, 10°→23°C, 2 h [Smith, W. N.; Beumel, O. F. *Synthesis*, **1974**, 441]).

(*Received in USA* 12 *June* 1995; *revised* 19 *July* 1995; *accepted* 21 *July* 1995)