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Syntheses of [5]-Helicene by McMurry or Carbenoid Couplings

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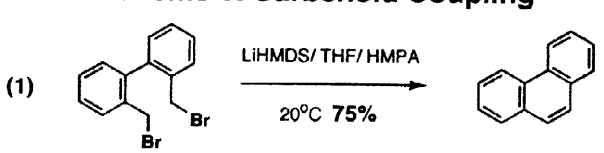
Abstract: Short syntheses of [5]-helicene have been accomplished under thermal conditions, without using photochemistry and high dilution. Key reactions comprised a McMurry coupling of a dialdehyde or a carbenoid-type coupling of aromatic bis(bromomethyl) moieties. The last coupling provided a 72% yield of [5]-helicene on a gram-scale (15 min., 0°C).

In 1967, Martin and coworkers elegantly synthesized [7]-helicene by photocyclodehydrogenation.[1] It is now the most widely used methodology to generate helicenes, but large scale preparations have been rare in the literature because of high dilution to prevent dimerization. On the other hand, the exploration of helicene chemistry in material sciences[2] and as ligands in catalysis would require a larger supply of product and short synthetic sequences.[3]

[5]-helicene was made in 1918 by a non-photochemical route.[4] Photocyclodehydrogenation to [5]-helicene generated benzo[g,h,i,]perylene as a major by-product if no "bromine auxiliary" is used.[5] New thermal methods overcame these limitations. Katz produced helicene-bisquinones by a Diels-Alder reaction.[6a] A Hewett cyclization was demonstrated in melted KOH (yields ~ 40-50%).[6b] Other efforts included oxidation of double phosphonium salts,[6c] Diels-Alder strategies,[6d] Wurtz-type coupling/Pd aromatization,[6e] Stevens rearrangement,[6f] Psorr reactions[1] and coupling of aromatic bis-bromomethyl moieties with KNH_2/NH_3 (l) (optimized 37% yield).[6g]

Recent carbenoid couplings for making enediynes,[7] the pioneered work of Kharash[8] and the work by Defay[6g] et al., inspired us here. We first tested the method of Jones[7] by an addition of LiHMDS to (1) and we obtained about 75% of phenanthrene (Scheme 1). We will then present one of the shortest gram-scale syntheses of [5]-helicene from commercial or prepared (2). A second sequence used the McMurry coupling of dialdehyde (7).

Scheme 1: Carbenoid Coupling



In Scheme 2, we used (±) (4) for the carbenoid couplings. We devised an efficient two-step synthesis of this compound from (±) (2) with MeMgBr in the presence of catalytic $NiCl_2$dppp.[9] An almost quantitative yield of (±) 2,2'-dimethyl-1,1'-binaphtyl was obtained (99% yield). We then undertook a radical bromination with NBS.[10] Compound (4) was recrystallized and shown to be almost exempt of mono-, tri- or tetrabromide, as determined by MS (EI) and ^{1}H NMR. These last two reactions could be produced near a gram-scale.

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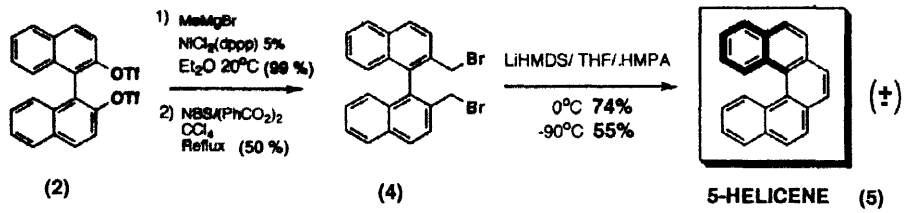
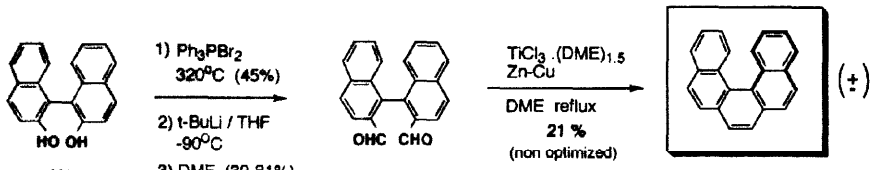
Scheme 2: Synthesis of (5)-Helicene by Carbenoid Coupling



(2) (4) 5-HELICENE (5)

The carbenoid coupling was first tried as described by Jones[7] with LiHMDS/THF/HMPA at -90°C but some dibromide remained unreacted along with [5]-helicene (55% yield). In another assay, the dibromide was added to an excess of a LiHMDS solution at 0°C (about a 10:1 molar ratio of base/dibromide). A bright yellow color appeared and [5]-helicene was spontaneously produced within 15 min. in a 72% isolated yield.

Scheme 3: Synthesis of (5)-Helicene by McMurry Coupling



(6) (7) (5)

A McMurry coupling in the formation of a heterohelicene prompted us to disclose our work on carbohelicenes.[11a] In Scheme 2, an intramolecular dialdehyde coupling of (7) was done under the most reproducible conditions with $TiCl_3.(DME)_{1.5}$ and Zn-Cu couple in refluxing DME.[12] One assay cleanly afforded a 21% yield of [5]-helicene but polar by-products were present. The dialdehyde precursor came from the conversion of ± (6) into ± 2,2-dibromo-1,1'binaphtyl[13] (~40-45% yield) followed by a double bromine-lithium exchange at low temperature with *t*-BuLi (2,2 eq) in THF and a quench with an excess of dry DMF. A 81% yield of dialdehyde (7) was obtained once but further improvements will be needed in this sequence.

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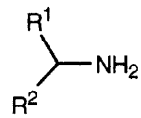
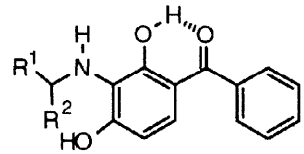
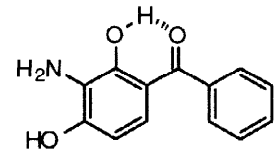
Table

Products and Yields of Controlled Potential Electrolyses of **1** in methanol containing an excess of amino alcohol or amine. E_{ox} = + 0.05 V s.c.e. ; E_{red} = - 1.5 V s.c.e.

Entry					
	R^1	R^2	Product	Yield %	**13**[a] Yield %
1	CH_2OH	Bu^t	**2**	65	-
2	CH_2OH	Pr^i	**3**	57	8
3	CH_2OH	Me	**4**	60	5
4	CH_2OH	CH_2OH	**5**	55	10
5	CH_2OH	Bzl	**6**	55	10
6	CH_2OH	H	**7**	60	22
7	Ph	Ph	**8**	37	23
8	Me	Me	**9**	50	17
9	Pe^i	H	**10**	35	30
10	Me	Pr^i	**11**	31	40
11	Pr^i	Pr^i	**12**	15	55

Abbreviations : tertiobutyl (Bu^t), isopropyl (Pr^i), isopentyl (Pe^i), Benzyl (Bzl).

[a] *Yield of compound **13** was probably higher than indicated because significant amounts were lost upon column chromatography due to its easy oxidation.*

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[8] A typical procedure was as follows : A solution of 2,3,4-trihydroxybenzophenone **1** (0.11g ; 0.5 mmol), lithium perchlorate (0.53g ; 5 mmol) and amino alcohol or amine (5 mmol) in methanol (250 mL) was oxidized under nitrogen at room temperature at + 0.05 V s.c.e. After exhaustive oxidation, i.e. when a steady-state minimum value of the current was recorded, the resulting solution was immediately reduced after the potential of the mercury pool was switched to - 1.5 V s.c.e. After exhaustive cathodic electrolysis, the solution was poured into a molar acetic acid-buffered aqueous solution of pH ~ 4.5 (100 mL). The resulting hydroalcoholic solution was concentrated to 100 mL under reduced pressure at 40°C and extracted with ethyl acetate (200 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent removed under reduced pressure at 40°C. The residue was chromatographed on silica, to give the expected 3,4-aminophenol derivatives.

3-[(2-hydroxy-1-tertiobutyl)-ethylamino]-2,4-dihydroxybenzophenone **2** : ^{1}H NMR (300 MHz, DMSO D_6) : δ 1.00 (s, 9H, Me, Bu^t), 3.30 (m, 1H, CH_2OH), 3.45 (m, 1H, CH-N), 3.60 (m, 1H, CH_2OH), 3.90 (broad s, 1H, NH, D_2O exchanged), 6.40 [d, 1H, H(5), J = 8 Hz], 6.85 [d, 1H, H(6), J = 8 Hz], 7.50 [m, 5H, benzoyl (1)], 12.80 [broad s, 1H, OH(2), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6) : δ 28.0 (Me, Bu^t), 35.8 (Cq, Bu^t), 63.0 (CH_2OH), 65.1 (CH-N), 109.2 (C-5), 113.1 (C-1), 126.4 (C-6), 126.6 (C-3), 129.4 [CH, meta, benzoyl (1)], 129.6 [CH, ortho, benzoyl (1)], 132.5 [CH, para, benzoyl (1)], 139.2 [Cq, benzoyl (1)], 155.0 and 155.1 (C-2 and C-4), 200.1 [CO, benzoyl (1)]. MS (DCI) : m/z = 330 (MH^+).

3-amino-2,4-dihydroxybenzophenone **13** : ^{1}H NMR (300 MHz, DMSO D_6) : δ 6.40 [d, 1H, H(5), J = 8 Hz], 6.75 [d, 1H, H(6), J = 8 Hz], 7.60 [m, 5H, benzoyl (1)], 10.20 [broad s, 1H, OH(4), D_2O exchanged], 12.20 [broad s, 1H, OH(2), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6) : δ : 108.3 (C-5), 113.0 (C-1), 124.0 (C-6), 125.0 (C-3), 129.3 [CH, meta, benzoyl (1)], 129.7 [CH, ortho, benzoyl (1)], 132.3 [CH, para, benzoyl (1)], 139.3 [Cq, benzoyl (1)], 151.8 and 151.9 (C-2 and C-4), 200.9 [CO, benzoyl (1)]. MS (DCI) : m/z = 230 (MH^+); m/z = 247 (MNH_4^+).

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