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Synthesis of *n*-Alkylnaphthalenes via Semicarbazones

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A number of 1-*n*-alkylnaphthalenes were prepared via the respective semicarbazones. The semicarbazones were reduced by modified Wolff-Kishner reductions to give 1-*n*-alkylnaphthalenes in excellent yields as manageable yellow or orange viscous oils. The semicarbazones were prepared from ketones, which are the addition products of Grignard reagents to nitriles. This study offers an excellent preparative method for the synthesis of 1-*n*-alkylnaphthalenes from semicarbazones, via a 3-step procedure.

Key Words: Alkylnaphthalenes, Semicarbazones, Wolff-Kishner reductions, Alkyl-1-naphthyl ketones, Grignard reaction.

Introduction

The preparation of 1-*n*-alkylnaphthalenes has presented a number of difficulties in the past. The popular Wurtz-Fittig aryl-alkyl coupling, which proceeds in the presence of sodium, provides fair yields of coupling products.[1]

The work of Jones and Gilman[2] offers another route for aryl-alkyl coupling using organolithium reagents in low polarity solvent mixtures. The halogen-metal interconversion reaction generally predominates when solvents having low polarity are used (Eq. 1). However, in high polarity solvent mixtures, aryl-alkyl coupled products are formed (Eq. 2). Numerous organolithium reactions are illustrated and discussed in detail by Wakefield.[3]

$$ArX + RLi \xrightarrow[\text{rt}]{\text{low polarity solvent}} ArLi + RX \quad (1)$$

$$ArX + RLi \xrightarrow[\text{rt}]{\text{high polarity solvent}} ArR + LiX \quad (2)$$

Improvements in this reaction were observed using more polar solvent mixtures as reported by Merrill and Negishi.[4] The reaction showed vast increases in yield, but still only to just a little over 80% at best. Moreover, 66% of *n*-butylnaphthalene was obtained in a tetrahydrofuran (THF)/hexane solvent mixture. Merrill and Negishi also reported problems with the formation of isomeric side-products.

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Kondolff et al. describe tetraphoshine/palladium Suzuki cross-coupling reactions for the synthesis of alkylnaphthalenes.[5] They use the palladium catalyst Pd-Tedicyp. Tedicyp is the new tetraphosphine ligand cis-cis-cis-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane. The ligand and the catalyst are prepared in their own laboratories.[6] Although they may use small amounts of the catalyst, the preparation of the ligand and the catalyst seems long and complicated. Our method is a lot more straightforward. The Grignard reagents used in our procedure are themselves easy to prepare,[7−9] and purification of the target products is much easier than that of reactions involving palladium catalysts. Moreover, Suzuki reactions have been used in our laboratories and have not been so pleasant to work with.

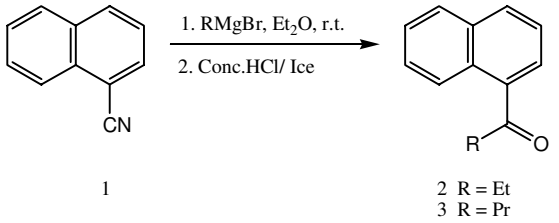
Morrell et al. prepared n-alkylnaphthalenes by Friedel-Crafts reactions of naphthalene with acid halides in nitrobenzene.[10] Nitrobenzene is very toxic and removal after the reaction is a terribly laborious process as experiences of Friedel-Crafts reactions using nitrobenzene in our laboratories have revealed. Their method seems primitive in this respect, and also with regard to purification as the workers purify the target alkyl naphthalenes via solid derivatizations. Additionally, no NMR data are presented.

Cagniant and Cagniant prepared n-alkylnaphthalenes by Wolff-Kishner reductions of the semicarbazone of n-alkyl 1-naphthyl ketone.[11,12] They made the ketone from a di-1-naphthyl cadmium reagent and the appropriate acyl chloride. However, cadmium and its compounds are hazardous and are known to be carcinogenic,[13] and so this method would not be such an attractive procedure to use. Our study provides a more convenient method of preparing the n-alkyl 1-naphthyl ketone.

This paper describes an improved synthesis of the 1-*n*-alkylnaphthalenes via their semicarbazones. The semicarbazones were prepared by an established procedure,[14] and the product was reduced by a modification of the Wolff-Kishner reduction.[15]

Results and Discussion

Following a procedure developed by Shriner and co-workers,[7] the Grignard reagent, alkylmagnesium chloride or bromide, was reacted with commercially available 1-naphthonitrile (**1**) in diethyl ether to prepare the alkyl 1-naphthyl ketones **2** and **3** (**Figure 1**). The Grignard reagent may be prepared by typical procedures using magnesium and alkyl halides,[7] or may be obtained commercially. The optimum conditions called for a ratio of Grignard reagent:nitrile to be 4:1. This large excess of the Grignard reagent seemed necessary in order to obtain good yields and avoid the formation of by-products as noted by Baerts.[16] Baerts proposed that the excess Grignard reagent converts the nitrile completely to the addition product, and hence there is less chance of polymeric by-products. These Grignard reactions proceeded cleanly to give excellent yields of the corresponding ketones. Grignard reactions are discussed in detail by Wakefield[8] and Silverman and Rakita.[9]



1 2 R = Et 3 R = Pr

Figure 1. Synthesis of alkyl 1-naphthyl ketones **1** and **2** via a Grignard reaction.

Ketones **2** and **3** were converted to their respective semicarbazones (**4** and **5**) by an established procedure,[14] and the product was reduced by a modification of the Wolff-Kishner reduction[15] to give the 1-*n*-alkylnaphthalenes (**6** and **7**) as viscous oils (**Figure 2**).

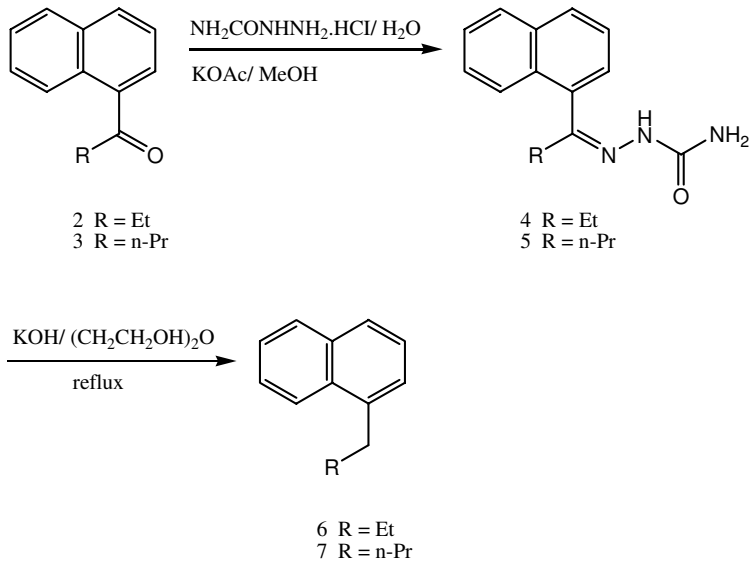


Figure 2. The conversion of ketones **2** and **3** to their respective semicarbazones (**4** and **5**) followed by reduction to the 1-*n*-alkylnaphthalenes **6** and **7**.

It is worth noting that the reaction time for the preparation of the n-propyl 1-naphthyl ketone semicarbazone (**5**) was very much greater than that used for the preparation of the ethyl analogue (**4**). The ethyl analogue required just warming of the alkyl 1-naphthyl ketone and semicarbazone mixture for product formation, whereas refluxing for 18 h was necessary for the n-propyl analogue. Furthermore, reduction of the n-propyl 1-naphthyl ketone semicarbazone (**5**) required stirring under reflux for 18 h, while heating the ethyl 1-naphthyl ketone semicarbazone (**4**) under reflux for 4.5 h was sufficient.

It may be hypothesized that a Sonogashira coupling reaction of 1-bromonaphthalene, using a palladium(0) catalyst could generate 1-alkynyl substituted naphthalenes quite easily.[17] Then standard catalytic hydrogenation would give the title compounds. However, this method is not only expensive, but also highly laborious. In addition, it is noteworthy that catalytic hydrogenation of compounds with naphthalene counterparts has proved to be difficult as mixtures of the starting material, the corresponding alkene and the desired alkane result.[18]

The Wolff-Kishner reduction procedures show the use of strongly basic conditions. This does not seem to pose a great problem and can be expanded to include other substituents. These conditions have been used on numerous occasions and the only cause for concern would be for carbonyl substituents, such as esters and amides.[18,19]

Experimental

General procedures: Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) data were recorded on a Bruker 300 AC

or JEOL 500 MHz spectrometer, using deuterated chloroform ($CDCl_3$) as the solvent. The NMR chemical shifts (δ) for both ^{1}H NMR and ^{13}C NMR data are presented in parts per million (ppm).

Infrared spectra were obtained either neat or as Nujol mulls between NaCl plates using a Nicolet 5DX Spectrometer or a Nicolet Magna-IR 550 Spectrometer and are reported in reciprocal centimeters (cm^{-1}). Mass spectral data were collected on a Hewlett-Packard 5890 or a Fisons GC 8000 Series Trio Gas Chromatography/Mass Spectrometer at 70 eV. Elemental analyses were carried out by Atlantic Microlabs Inc., Atlanta, GA, USA. High resolution mass spectra were provided by the Mass Spectrometry Laboratory at the University of Illinois.

The solvent diethyl ether was distilled from sodium benzophenone-ketyl immediately before use. Methanol was distilled from Mg^0/I_2 and stored over Type 4Å molecular sieves. Commercially available (Aldrich) solutions of Grignard reagents were standardized by titration with menthol and 1,10-phenanthroline.[20]

All reactions were carried out under an atmosphere of argon or nitrogen gas. Reaction temperatures were measured either externally or by a thermometer inserted into the reaction mixture. Universal silica gel was used for all column chromatography and E. Merck silica gel for thin-layer chromatography.

Ethyl 1-Naphthyl Ketone (2): To a solution of 50.0 mL (3.0 M solution in diethyl ether, 0.15 mol) of ethylmagnesium bromide, 5.58 g (36.41 mmol) of 1-cyanonaphthalene (**1**) in 15.0 mL of dry diethyl ether was added slowly, with stirring, over 15 min. The solution was stirred for 1 h longer and allowed to stand overnight. The mixture was carefully poured onto a mixture of 72.5 g of ice and 43.5 mL of concentrated HCl. The water layer, which contained the hydrochloride of the ketimide, was separated from the ether layer and heated at vigorous reflux for 1 h. The solution was cooled and extracted with diethyl ether. The ether extract was dried over $MgSO_4$ and concentrated by evaporation in vacuo. The crude product was purified by Kugelrohr distillation (190 °C/1.0 mmHg) to yield 6.50 g (97%) of the desired product as a yellow oil, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, J=7.3 Hz, 3H), 2.78 (q, J=7.0 Hz, 2H), 7.47-7.62 (m, 3H), 7.84-7.88 (m, 2H), 7.98 (d, J=8.2 Hz, 1H), 8.67 (d, J=8.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.6, 35.4, 124.4, 125.8, 126.4, 127.1, 127.7, 128.4, 130.1, 132.3, 133.9, 136.2, 205.3; IR (neat) 1675 cm^{-1}; GC/ MS (EI) m/z (relative intensity) 184 (20), 155 (100), 127 (92).

n-Propyl 1-Naphthyl Ketone (3): n-Propyl 1-naphthyl ketone (3) was prepared from *n*-propylmagnesium chloride and 1-cyanonaphthalene (1) as described above. From 50.00 mL (2.0 M solution in diethyl ether, 0.10 mol) of *n*-propylmagnesium chloride and a 3.72 g (24.30 mmol) solution of 1-cyanonaphthalene (1) there was obtained, after purification by Kugelrohl distillation (235 °C/ 1.0 mmHg), 4.34 g (90%) of the desired product (3) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J=7.4 Hz, 3H), 1.83 (q, J=7.3 Hz, 2H), 3.03 (t, J=7.3 Hz, 2H), 7.46-7.62 (m, 3H), 7.82-7.88 (m, 2H), 7.96 (d, J=8.2 Hz, 1H), 8.59 (d, J=8.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 18.1, 44.1, 124.3, 125.7, 126.3, 127.1, 127.7, 128.3, 130.0, 132.3, 133.9, 136.2, 205.3; GC/ MS (EI) m/z (relative intensity) 198 (20), 155 (100), 127 (80), 101 (6), 77 (11).

Ethyl 1-Naphthyl Ketone Semicarbazone (4): The semicarbazone reagent was prepared by dissolving 8.15 g (73.05 mmol) of semicarbazide hydrochloride in 19.0 mL of water and adding to this a solution of 12.19 g (0.12 mol) of potassium acetate in 48.0 mL of methanol. The potassium chloride thus formed was filtered out after 30 min, leaving the semicarbazone reagent solution as the filtrate. In a second

reaction, a solution of 5.25 g (28.50 mmol) of ethyl 1-naphthyl ketone (2) in 23.4 mL of methanol was treated with 17.7 mL of the semicarbazone reagent prepared earlier. The mixture was warmed on a hot water bath until crystallization began. Crystallization was allowed to continue at room temperature. The product was filtered and dried under vacuum to give white crystalline semicarbazone 6.20 g (90%), which showed satisfactory purity and was used for the next step without further purification: m.p. 175-177 °C (lit.[21] 219 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, J=7.6 Hz, 3H), 2.75 (q, J=7.6 Hz, 2H), 6.13 (br s, 1H), 7.47 (s, 2H), 7.50-7.53 (m, 4H), 7.86-7.93 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.8, 24.3, 125.2 125.8, 126.0, 126.5, 127.0, 128.5, 128.8, 131.3, 133.8, 136.5, 152.6, 157.9; GC/ MS (EI) m/z (relative intensity) 241 (12), 197 (32), 182 (100), 167 (76), 153 (53), 127 (34), 115 (16).

n-Propyl 1-Naphthyl Ketone Semicarbazone (5): n-Propyl 1-naphthyl ketone semicarbazone (5) was prepared from semicarbazone reagent solution and propyl-1-naphthyl ketone (4) as described above. From a mixture of 16.0 mL of semicarbazone reagent and 4.74 g (23.91 mmol) of n-propyl 1-naphthyl ketone (4) in 19.7 mL of methanol there was obtained, after 18 h of stirring under reflux followed by purification, 5.70 g (93%) of white crystalline semicarbazone. The semicarbazone reagent solution was prepared as described above from 7.35 g (65.91 mmol) of semicarbazide hydrochloride in 17.1 mL of water and 11.00 g (0.11 mol) of potassium acetate in 43.0 mL of methanol: m.p. 165-167 °C (lit.[22] 170-172 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=7.3 Hz, 3H), 1.47-1.69 (m, 4H), 6.13 (br s, 1H), 7.17 (s, 2H), 7.50-7.59 (m, 4H), 7.84-7.92 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 19.7, 40.7, 124.4, 125.0, 125.5, 126.7, 127.4, 128.8, 129.6, 131.6, 133.7, 136.8, 156.7, 158.0; GC/ MS (EI) m/z (relative intensity) 255 (11), 211 (36), 196 (100), 167 (88), 153 (67), 127 (40), 115 (20).

1-*n*-Propylnaphthalene (6): A solution of 32.10 g (0.57 mol) of powdered KOH in 236.0 mL of diethylene glycol was prepared. After cooling the solution to 40 °C, 5.00 g (20.72 mmol) of ethyl 1-naphthyl ketone semicarbazone (**4**) was added. The reaction mixture was stirred under reflux for 4.5 h. After cooling to 80 °C, the reaction mixture was diluted with 20.0 mL of water and extracted with hexanes. The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed by evaporation in vacuo to yield 3.38 g (96%) of the desired product as an orange oil: bp 274 °C/ 760 mmHg (lit.[23] bp 275-276 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J=7.4 Hz, 3H), 1.77-1.85 (m, 2H), 3.09 (t, J=7.7 Hz, 2H), 7.35-7.50 (m, 2H), 7.52-7.57 (m, 2H), 7.75 (d, J=8.2 Hz, 1H), 7.89 (d, J=7.5 Hz, 1H), 8.09 (d, J=7.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 23.9, 35.1, 123.9, 125.3, 125.5, 125.6, 125.9, 126.4, 128.7, 131.9, 133.9, 138.7; GC/ MS (EI) m/z (relative intensity) 170 (28), 141 (100), 115 (4).

1-*n*-Butylnaphthalene (7): 1-*n*-Butylnaphthalene (**7**) was prepared from n-propyl 1-naphthyl ketone semicarbazone (**5**) as described above. From a mixture of 72.84 g (0.32 mol) of powdered KOH in 131.0 mL of diethylene glycol and 2.94 g (11.52 mmol) of n-propyl 1-naphthyl ketone semicarbazone (**5**) there was obtained, after 18 h of stirring under refux followed by purification, 2.00 g (94%) of the desired product as an orange oil: bp 292 °C/ 760 mmHg (lit.[24] bp 289 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J=7.3 Hz, 3H), 1.47-1.60 (m, 2H), 1.79-1.86 (m, 2H), 3.14 (t, J=7.8 Hz, 2H), 7.38-7.49 (m, 2H), 7.51-7.60 (m, 2H), 7.77 (d, J=8.1 Hz, 1H), 7.92 (d, J=7.4 Hz, 1H), 8.13 (d, J=7.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.9, 32.8, 33.0, 123.9, 125.3, 125.5, 125.6, 125.8, 126.4, 128.7, 131.9, 133.9, 138.9; GC/ MS (EI) m/z (relative intensity) 184 (23), 141 (100), 115 (28).

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