A NEW SYNTHESIS OF 1-ALKYL(ARYL)-4-ISOQUINOLINOLS

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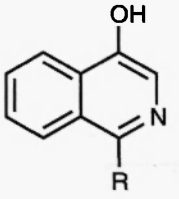
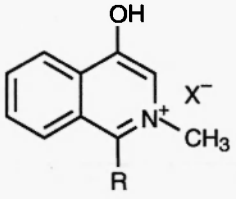
Abstract

A new synthesis of 4-isoquinolinol and 1-methyl-4-isoquinolinol and its application to the syntheses of other 1-alkyl(aryl)-4-isoquinolinols from 4-bromoisoquinoline was developed.

We recently required a method for synthesizing 1-substituted 4-isoquinolinols 1. N-methyl-4-hydroxyisoquinolinium salts 2, which are derived from the corresponding 4-isoquinolinols 1 can be converted to benzocycloheptenes-5,8-imines 3 by methodology previously developed by Katritzky (1) and used in our laboratory (2). The related compound MK801 4a and other 5-substituted benzocycloheptenes-5,8-imines 4b have been shown to be effective anticonvulsants (3). Surprisingly, we found only two reported methods for synthesizing the 1-substituted 4-isoquinolinols 1: (i) the rearrangement of isoquinoline N-oxides (4, 5, 6, 7, 8) and (ii) the air-oxidation of 1,2-dihydroisoquinolines (9). We report here an efficient synthesis of 1-substituted 4-isoquinolinols 1 that has been used to conveniently prepare gram quantities of the title compounds in good yield.



1, R = alkyl or aryl substituent



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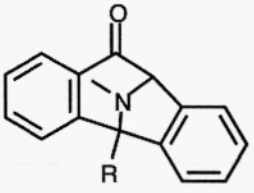

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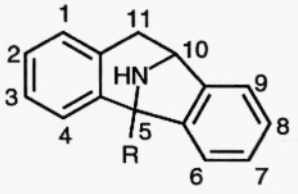


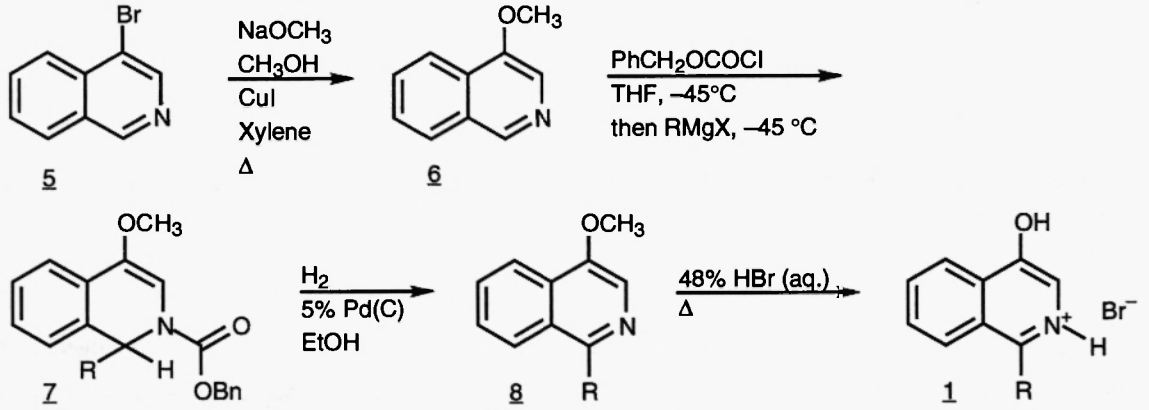
4a, R = CH_3
b, R = $CONH_2$

The methodology is based on chemistry that has been used for functionalizing the 2 position (10) of pyridine (11, 12, 13). The reaction of pyridine with an alkyl or aryl chloroformate followed by treatment of the resulting 1-acylpyridinium salt with a Grignard reagent leads to the corresponding 2- and/or 4-substituted 1-acyldihydropyridines depending on the conditions of the reaction and the pyridine substrate. The dihydropyridines can either be utilized for preparing piperidine natural products (14) or aromatized to the corresponding substituted pyridines (12). A limited number of isoquinolines, none possessing a 4-hydroxyl group, have been functionalized in a similar manner to give 1-substituted (10) 2-acyl-1,2-dihydroisoquinolines (15). This methodology appeared to be ideal for introducing the requisite 1-alkyl(aryl) substituent of

the 4-isoquinolinols 1. We reasoned that the C-4 hydroxy group could be introduced by using 4-methoxyisoquinoline 6 as starting material with subsequent removal of the methyl protecting group after introduction of the 1-substituent.

4-Methoxyisoquinoline 6 has been synthesized from commercially available 4-bromoisoquinoline 5 in 47% yield by heating (165 °C) the aryl bromide in a methanolic solution of copper (II) chloride and sodium methoxide in a bomb (16). We found a more convenient and higher yielding method based on a modification of Bacon's alkyl aryl ether preparation (17, 18). Thus, 4-bromoisoquinoline 5 was methoxylated (Scheme 1) with sodium methoxide using copper (I) iodide in refluxing xylene to give 4-methoxyisoquinoline 6 in 80% yield.

Scheme 1. Synthesis of 1-Substituted 4-Isoquinolinol (1) Hydrobromides



a, R = CH_3 c, R = *i*-Pr
b, R = Et d, R = Ph

Isoquinoline 6 is an important intermediate because the correct oxidation state at C-4 is established while giving a compound that can be further functionalized at C-1 with organometalic reagents. Treatment of 6 with benzyl chloroformate followed by reaction of the resulting 2-acylisoquinolinium salt with methyl, ethyl, isopropyl, or phenyl magnesium halide gave the corresponding 1-substituted 2-acyl-1,2-dihydroisoquinolines 7a-d. Catalytic hydrogenation of carbamates 7a-d effected removal of the carbobenzyloxy group and subsequent aromatization to give 1-substituted 4-methoxy isoquinolines 8a-d (64-81% yield from 6, Table I). Isoquinolines 8a-d were purified for characterization

Table I. Percent Yield and MPs for 1-Substituted 4-Methoxyisoquinolines 8

Compound	R	mp, °C	% Yield[a,b]
8a	Me	38-39	75
8b	Et	27-28	64
8c	*i*-Pr	Oil	81
8d	Ph	78-80	71

[a] Isolated yield from 6 after flash chromatography. [b] 8a-d gave spectral properties consistent with the proposed structure and gave satisfactory C, H, N analysis (±0.4).

purposes but could be used directly in the final step. Conversion of 8a-d as well as 6 to the desired 4-isoquinolinol hydrobromides 1a-e proceeded smoothly in refluxing 48% aqueous hydrobromic acid in near quantitative yield (90-98% yield after recrystallization, Table II).

Table II. Percent Yield and MPs for 1-Substituted 4-Isoquinolinols 1

Compound	R	mp, °C	% Yield[a,b]
1a	Me	188-189	96[c]
1b	Et	246-248 (darkens)	98
1c	*i*-Pr	234-235	90
1d	Ph	260 (dec)	92[d,f]
1e	H	188-189	98[e,f]

[a] Isolated yield from 8 after recrystallization. [b] Compounds 1a-e gave spectral properties consistent with the proposed structure and gave satisfactory C, H, N analysis (±0.4). [c] When converted to its free base, 1a had mp 200-205 °C (dec) [lit.(9) mp 199-201 (subl.)]. [d] When converted to its free base, 1d had mp 244-248 °C (dec) (lit.(19) mp 248-251 °C). [e] When converted to its free base, 1e had mp 211-216 °C (dec) (lit.(20) mp 210-214 °C). [f] C, H, N analysis for 1d was $C_{15}H_{12}BrNO \cdot 0.25\ H_2O$ and for 1e was $C_9H_8BrNO \cdot 0.25\ H_2O$.

In summary, a convenient and high yielding synthesis of 1-alkyl(aryl)-4-isoquinolinols has been accomplished from readily available 4-bromoisoquinoline. This route appears general and lends itself to large scale synthesis as no chromatography of intermediates or products is necessary.

The following procedure is representative. Benzyl chloroformate (7.65 g, 0.045 mol) was added dropwise to a stirred solution of 4-methoxyisoquinoline 6 (18) (5.10 g, 0.032 mol) in 150 mL of dry tetrahydrofuran at -45 °C (dry ice acetonitrile). After 30 min, 32.0 mL of methyl magnesium bromide (3.0 M, 0.096 mol) was added dropwise at the same temperature. The mixture was allowed to stir for 1 h, quenched with 50 mL of saturated ammonium chloride, and the volatiles were removed at reduced pressure. Water was added and the resulting aqueous layer was extracted with methylene chloride. The combined methylene chloride layers were washed with water and brine. After drying the organic layer over sodium sulfate, the volatiles were removed under reduced pressure to give 10.55 g of the dihydro product 7a.

To a solution of 7a from above in 200 mL of absolute ethanol was added 2.19 g of 5% palladium on carbon. This mixture was hydrogenated (1 atm) at room temperature until TLC (hexane/ethyl acetate, 4:1) indicated the reaction was complete (4 h). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give 5.73 g of 4-methoxy-1-methylisoquinoline 8a.

A solution of 8a from above in 150 mL of hydrobromic acid (48% aq.) was heated to reflux for 16 h. The solution was cooled and the volatiles were removed at reduced pressure. Recrystallization of the resulting solid from ethyl acetate/methanol (1:1) gave 5.75 g (75% from 4-methoxyisoquinoline) of 1-methyl-4-isoquinolinol hydrobromide 1a. When converted to its corresponding free base, 1a had mp 200-205 °C (dec) [lit. (9) mp 199-201 °C (subl.)]. The ^1H and ^{13}C NMR resonances were identical to those reported (9).

Acknowledgment

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