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SYNTHESIS OF 1,4-DISUBSTITUTED ISOQUINOLINES AS CHERYLLINE DERIVATIVES

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Abstract

Synthetic studies of aryl-l,2,3,4-tetrahydroisoquinolines have attracted much attention from the synthetic community owing to the potential biological activities of this class of compounds and their increasing medicinal interest. The alkaloid cherylline is a naturally occurring optically active, 4-aryl-1,2,3,4- tetrahydroisoquinoline alkaloid, isolated from Crinum Powellii, Amaryllidaceae plant. There are many ways for cherylline synthesis. An application of Bischler-Napieralski reaction for the synthesis of new 1,4-disubstituted- 1,2,3,4-tetrahydroisoquinolines as cherylline derivatives, is described.

Key words: *cherylline, 1,4-disubstituted-tetrahydroisoquinolines, Bischler-Napieralski reaction*

INTRODUCTION

Nitrogen containing heterocycles comprise a major portion of natural and unnatural compounds of important biological activity [1-6]. Isoquinolines and their dihydro derivatives attract much attention owing to their potential pharmacological activity [7]. Important examples of this class of compounds are kibdelones A-C [8-9], fredericamycin A [10], and alternarlactam [11]. Tetrahydroisoquinoline is also an interesting structural motif that appears in a number of biologically active compounds [12]. 4-Aryltetrahydroisoquinolines are of interest because of their various pharmacological activities [13].

Cherylline is 4-aryl-tetrahydroisoquinoline alkaloid isolated from *Crinum powellii*, *Crinum moorei*, and other *Crinum* species. The genus *Crinum* belongs to the *Amaryllidaceae* family and comprises approximately 160 species distributed throughout the tropics and warm temperate regions of the world in Asia, Australia, Africa and America [14]. Total extracts of *Crinum* species exhibit different biological activities. Thus, an extract of *Crinum macowanii* showed in vitro activity against exotic RNA viruses [15]. The water-extract of *Crinum asiaticum* var. *siacum* showed strong inhibitory activity of calprotectin-induced apoptosis[16], the main active compound is lycorine. The alcoholic extract from *Crinum jagus* possessed antibacterial activity, but no antifungal activity[17] Renard–Nozaki and co-workers reported in their study for the relationship between the structure of *Amaryllidaceae* alkaloids and antiviral activity that *cherylline*-type compounds: *Cherylline* **1**, Dimethylcherylline **2**, *Latifine* **3**, Dimethyllatifine **4 (**Figure 1**)** with a 4-phenylisoquinoline ring are not toxic at all [18].

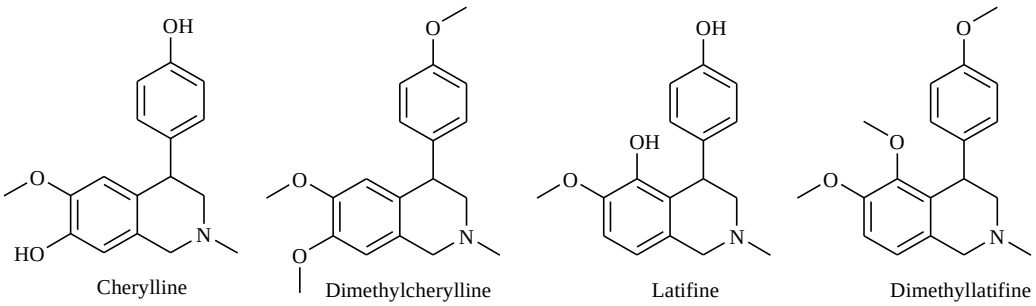
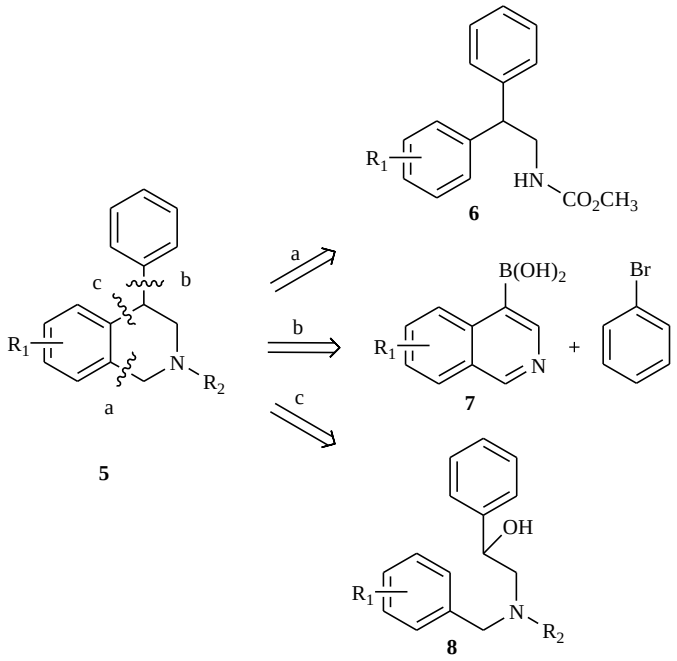


Figure 1.

There are a number of existing methods to build 4-substituted tetrahydroisoquinolines. Several of them, shown on Scheme 1, include: a) Bischler-Napieralski cyclisation of **6;** b) a Suzuki coupling between boronic acid **7** and an aryl halide, followed by a reduction sequence [19-21] and c) intramolecular Friedel-Craft cyclisation of a benzylic alcohol **8**.

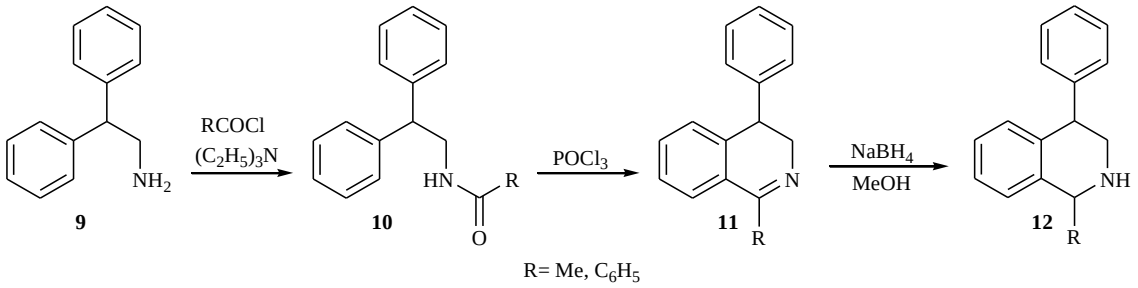


Scheme 1. Main routes for 4-aryl-tetrahydroisoquinolines synthesis

During the years there are many reports related with *cherylline* synthesis. Katakawa and co-workers reported synthesis of (±)-*cherylline* **1** and (±)-*latifine* **3** by application of an isocyanate cyclization reaction according to Tsuda's two step procedure for constructing 1,2,3,4-tetrahydroisoquinolinol-1-one and a regioselective cleavage reaction of aromatic methyl ethers with dimethyl sulphide in methanesulfonic acid [22]. Couture, A. et al., reported a new approach for synthesis of *cherylline* [23]. Their strategy hinges upon the remarkable nucleophilicity of phosphorylated α-aminocarbanions and their ability to generate inter and intramolecularly the easily reducible N-C=C unit in a variety of open chain or annulated adducts. Initially the dimethoxyphthalic anhydride readily accessible by oxidation of *m*-meconine was opened by Friedel-Crafts reaction with anisole to afford *o*-aroyldimethoxybenzoic acid derivative. Honda, Namiki and Satoh reported synthesys of *cherylline* and *latifine* using palladium-catalyzed intramolecular *δ*-Lactam formation of aryl halides and amide-enolates [24]. Raju, Neelakantan and Bhalerao reported a synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines by in situ generation of *p*-quinone methides resulting in a novel C-C bond formation [25]. Quinone methides are interesting compounds and play an important role in biosynthesis and in the biological activity of many quinonoid antitumor compounds. However, synthetic methodologies to produce such quinone methides and their applications are limited because in situ generated *o*-quinone methides acting as hetero-dienes in Diels-Alder reactions [26-28]. David J. Hart and co-workers' reported the synthesis and chemistry of *p*-quinone methide ketals, prepared from *p*-quinone monoketals and α-trimethylsilylamides or phosphoranes within the context of the total synthesis of *Amaryllidaceae* alkaloid *cherylline* [29]. Jose Crecente-Campo reported [30] an efficient and simple procedure for the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolones and 1-aryl-2,3,4,5-tetrahydro-3-benzoazepines. The approach uses easily available starting materials and requires just three steps. The hydroamination of an enol carbamate is the key step. This general and direct method has been applied to the total synthesis of the natural alkaloid *cherylline* and to biologically active 3-benzoazepines as well. Stephane Lebrun and co-workers reported a synthesis of (+)- and (-)-*cherylline*[31]. They devised a concise synthesis of enantiopure antipodes of alkaloid *cherylline*. The synthetic strategy relies upon the reduction of a diversely and polyprotected diarylamine bearing a chiral auxiliary. Separation of diastereopure intermediates, concomitant deprotections and intramolecular reductive amination complete the synthesis of the natural (*S*)-enantiomer and the unnatural (*R*)-configured antipode.

RESULTS AND DISCUSSION

In a search of new approaches for synthesis of 1,4-disubstituted tetrahydroisoquinolines, as *cherylline* derivatives, we found that they can be obtained from corresponding amides **10** in very good yields. The required amides **10** we prepared by acylation of 2,2-diphenylethanamine **9** (commercially available) with acetyl chloride and benzoyl chloride. In our previous reports [32-33], we have shown that the reaction of amides in the presence of phosphoryl chloride affords the corresponding 1-substituted-4-aryl-3,4-dihydroisoquinolines. (Scheme 2, Table 1).



Scheme 2.

	R	Yield, %	mp, °C
10a	CH_3	98	85-86
10b	C_6H_5	94	143-145
11a	CH_3	85	Oil
11b	C_6H_5	82	126-127
12a	CH_3	83	Oil
12b	C_6H_5	82	Oil

Table 1. Yields of amides 10, dihydroisoquinolines 11 and tetrahydroisoquinolines 12*

*For all compounds **10**, **11** and **12**: a) R=CH_3; b) R=C_6H_5.

The next step in our synthesis was reduction of obtained 1-substituted-4-aryl-3,4-dihydroisoquinolines **11**. We applied simple reduction of 3,4-dihydroisoquinolines to corresponding 1,2,3,4-tetrahyroisoquinolines using sodium borohydride. Sodium borohydride under normal conditions reduced (in moderate to good yields) double bonds in compounds, where the double bonds are cross-conjugated with carboxylic groups or phenyl group. In this cases the reduction was carried out by allowing equimolar quantities of sodium borohydride and 3,4-dihydroisoquinoline **11** in ethanol or isopropyl alcohol to react first at 0-5ºC and then at rt [34]. We found that this reduction easily obtained corresponding 1,2,3,4-tetrahyroisoquinolines **12** using methanol as solvent with 82-83% yields (Table 1).

EXPERIMENTAL SECTION

Reagents and chemicals were purchased from commercial sources [Fluka and Merck] and used as received. Melting points were determined on a Boetius hostage apparatus and are uncorrected. Spectra were recorded on a Bruker Avance DRX250 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ (unless otherwise specified) at 250 or 600 MHz and 62.5 MHz respectively. Chemical shifts were given in part per million (ppm) relative and were referenced to TMS (□=0.00ppm) as an internal standard and coupling constants are indicated in Hz. All the NMR spectra were taken at rt (ac. 295 K). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates. Merck silica gel 60 (0.063-0.2mm) was used for column chromatographic separation.

2, 2-diphenylethanamine 9 - commercially available.

Synthesis of amides 10, typical procedure:

To the solution of 1 mmol of 2, 2-diphenylethanamine **9** in dichloromethane equal amount of acetyl chloride or benzoyl chloride was added. After 10 min a little excess of triethylamine was added. After 30 min the solution was washed subsequent with diluted hydrochloric acid, saturated solution of Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), filtered on short column with neutral Al_2O_3 and after removing of the solvent, the pure product **10** was isolated.

N-(2,2-diphenylethyl)acetamide 10a – known compound [35,36]

N-(2,2-diphenylethyl)benzamide 10b [35, 37, 38] - ^{1}H-NMR: 4.01 (dd, 2H, J=5.9, 7.9, CH_2), 4.25 (t, 1H, J=7.9, CH), 6.04 (t, 1H, J=5.8, NH), 7.12-7.20 (m, 3H, Ar), 7.21-7.22 (m, 5H, Ar), 7.23-7.30 (m, 4H, Ar), 7.32-7.39 (m, 1H, Ar), 7.47-7.51 (m, 2H, Ar); ^{13}C-NMR: 167.5, 141.9, 134.6, 131.4, 128.8, 128.6, 128.1, 127.0, 126.8, 50.6, 44.3.

Cyclisation of amide 10 to 3,4-dihydroisoquinolines 11, typical procedure:

Solution of 1 mmol of amides **10** in 3 ml phosphorus oxychloride was refluxed for 30 minutes. The cool reaction mixture was washed with saturated solution of Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), filtered on short column with basic Al_2O_3 and after removing of the solvent, the pure product with high yield was isolated.

1-methyl-4-phenyl-3,4-dihydroisoquinoline 11a [37] - ^{1}H-NMR: 1.81 (s, 3H, CH_3), 3.82 (dd, 2H, J=5.8, 7.99, CH_2), 3.95-3.98 (m, 1H, CH), 7.14-7.18 (m, 5H, Ar), 7.21-7.24 (m, 2H, Ar), 7.47-7.50 (m, 2H, Ar); ^{13}C-NMR: 152.9, 141.9, 131.0, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 127.4, 127.1, 126.9, 126.6, 125.4, 54.1, 42.4, 23.4.

1,4-diphenyl-3,4-dihydroisoquinoline 11b Known compound [38-40].

General procedure for reduction of 3,4-dihydroisoquinoline 11 to 1,2,3,4-tetrahydroisoquinolines 12, typical procedure:

To solution of 1 mmol of the 3,4-dihydroisoquinoline **11** in 15 mL methanol, $NaBH_4$ (2 mmol, 0,1 g) was added portionwise. The solution was stirred 30 min at room temperature, then the solvent was removed under vacuum. Water (30 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3x20 mL), then the combined extracts were dried (Na_2SO_4). The products, after evaporation of the solvent, were obtained with high yields.

1-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 12a – ^{1}H-NMR: 1.45 (d, 3H, J=6.7, CH_3), 1.78 (s, 1H, NH), 3.14 (dd, 1H, J=4.99, 5.9, CH_2), 3.24 (dd, 1H, J=4.7, 13.2, CH_2), 4.01 (dd, 1H, J=6.9, 11.5, CH-C1), 4.10 (dd, 1H, J=5.9, 6.2, CH-C4), 7.02 (dd, 1H, J=1.8, 6.7, Ar), 7.09-7.13 (m, 4H, Ar), 7.17-7.19 (m, 4H, Ar); ^{13}C-NMR: 144.2, 143.6, 142.0, 141.0, 140.1, 139.8, 135.7, 129.3, 128.9, 127.9, 125.8, 125.2, 50.6, 48.5, 43.9, 21.9.

1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline 12b - ^{1}H-NMR: 2.24 (broad s, 1H, NH), 4.02 (dd, 1H, J=5.8, 7.9, CH_2), 4.25 (t, 1H, J=8.0, CH_2), 5.14-5.21 (m, 1H, CH-C4), 5.98 (s, 1H, CH-C1), 7.13-7.19 (m, 5H, Ar), 7.22-7.23 (m, 4H, Ar), 7.26-7.29 (m, 5H, Ar); ^{13}C-NMR: 140.8, 130.4, 128.1, 127.8, 127.5, 127.4, 127.2, 127.1, 125.9, 125.8, 49.5, 43.3, 20.2.

CONCLUSION

In conclusion, six-membered nitrogen-bearing heterocycles, as *cherylline* skeleton were synthesized, as compounds found in nature and among bioactive compounds of interest. We have developed a convenient method for their synthesis using Bischler-Napieralski reaction as key step and simple reduction of obtained 3,4-dihydroisoquinolines in sodium borohydrode-methanol system.

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