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Oxazoline as a useful tool in organic synthesis: preparation of 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid skeleton

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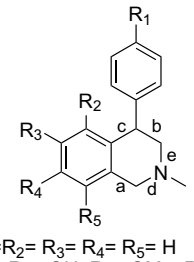
Abstract—New direct strategy for the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines. The key steps are based on oxazoline chemistry: nucleophilic substitution in an *ortho*-methoxyphenyloxazoline with a Grignard reagent and a 1,6-conjugate addition of a lithium amide to *o*-styrylphenyloxazoline.

The 4-aryl-1,2,3,4-tetrahydroisoquinoline system (**1**) has attracted attention not only because of its physiological activities,[1–4] but also owing to its presence as a basic skeleton (**1a**) in many natural products and drugs. These include nomifensine (**1d**),[5] and infrequent phenolic Amaryllidaceae alkaloids[6] such as cherylline (**1b**)[7] isolated from *Crinum powelli*, and latifine (**1c**)[8] isolated from *Crinum* latifolium. This genus has been used in Vietnamese and Chinese traditional medicine as a rubefacient, tonic, and for treatment of allergic disorders and tumor diseases.[9,10]

Due to the increasing medicinal interest of this family of compounds, several syntheses of this skeleton have been published. They can be sorted by the nature of the bond formed in the heterocyclic ring closure (Fig. 1). Thus, (i) the C–C bond '*a*' was caused by a Bischler–Napieralski reaction of *N*-formyl derivatives of phenethylamines[11–13] or by cyclization of β-phenethylisocyanates;[14,15] (ii) the C–C bond '*b*' was mainly formed by intramolecular Horner reaction;[16] (iii) the C–C bond '*c*' was achieved by several methods, such as photoinduced cyclization of *ortho*-halogenated *N*-acylbenzylamines,[17] Friedel–Crafts type reactions,[18–24] intramolecular coupling of quinonoid intermediates[25–28] or palladium-catalyzed intramolecular cyclization of amide-enolates;[29] (iv) finally and less usually, the C–N bonds '*d*' or '*e*' were constructed mostly by N-alkylation.[30,31]

Previously, we have described the utility of the hydroamination of styrenes in the synthesis of β-phenylethylamines based on the addition of lithium[32] or potassium[33] amides to styrenes. This strategy seems to be suitable for the development of a convenient method for the synthesis of the 4-aryl-1,2,3,4-tetrahydroisoquinoline skeleton. Therefore, in this paper, we disclose a simple and powerful synthetic approach to isoquinoline alkaloids based on the formation of '*c*' and '*e*' bonds mediated by nucleophilic additions—both of which rely on oxazoline chemistry—affording a simple and easy formation of '*d*' bond as the final step. Thus, the strategy consists of the formation of a 1,1-diphenyl ethylene derivative from the nucleophilic displacement of an



1a, R_1=R_2= R_3= R_4= R_5= H
1b, R_1= R_4= OH, R_3= OMe, R_2=R_5= H
1c, R_1= R_2= OH, R_3= OMe, R_4= R_5= H
1d, R_5= NH_2, R_1= R_2= R_3=, R_4= H

Figure 1.

Keywords: 4-Aryl-1,2,3,4-tetrahydroisoquinoline; 1,6-Conjugate addition; 2-Oxazoline.
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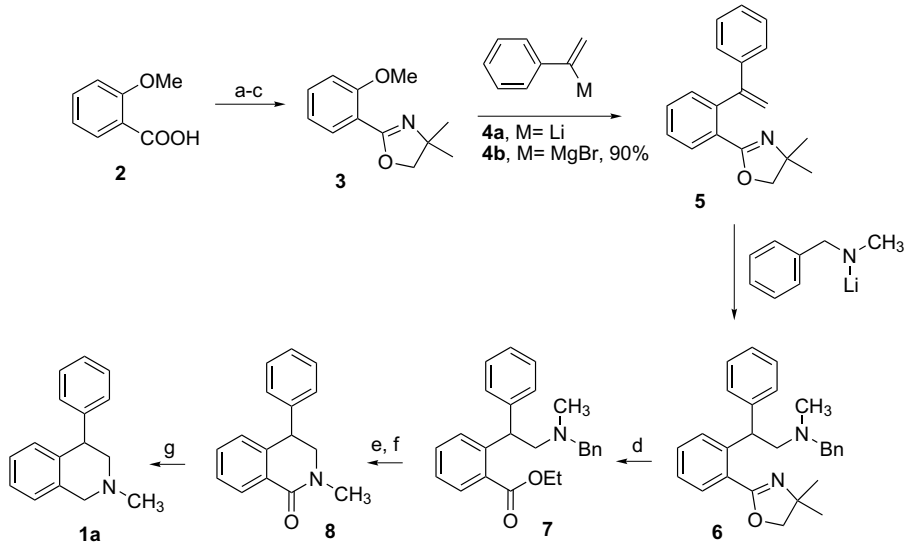

Scheme 1. Reagents and conditions: (a) $SOCL_2$; (b) $H_2NMe_2CCH_2OH$; (c) $SOCl_2$; (d) 20% H_2SO_4/EtOH, reflux, 63%; (e) 10% AcOH/EtOH, H_2, 5% Pd–C (50 psi); (f) AcONa/EtOH, reflux, 80% over two steps; (g) $LiAlH_4$, THF, reflux, 92%.

ortho-methoxy group in a *o*-styrylphenyloxazoline with a β-styryl organometallic reagent, followed by a 1,6-conjugate addition[34] of a lithium amide to a 2-(1-phenylvinyl)phenyl-2-oxazoline to introduce the nitrogen atom (Scheme 1). Thus, the target for the hydroamination would be a 1,1-diphenylethylene derivative with an *ortho* carboxylic group in one of the aromatic rings. This carboxylic group can be masked as a 2-oxazoline, since this ring has been shown to be compatible with the reaction conditions for hydroamination of styrenes with an additional enhancing effect as regards the free carboxylic group.[35] Furthermore, the presence of the oxazoline group allows the preparation of the 1,1-diphenylethylene derivative **5**, by the nucleophilic displacement of an *ortho*-methoxy group to the oxazoline.

Oxazoline **3** was prepared from 2-methoxybenzoic acid (**2**), as previously described (83% yield).[36,37] The nucleophilic displacement of the *ortho*-methoxy group,[36] to introduce the 1-phenylvinyl group, was carried out using an adequate organolithium reagent. However, the addition of organolithium **4a**—prepared from a reaction of *n*-BuLi with commercial α-bromostyrene—to oxazoline **3** failed. Previous studies on the chemistry of 2-aryloxazolines,[36] show that the displacement of the *ortho*-methoxy group can be achieved by using Grignard reagents. Usually, the reactivity is complementary as we have recently proved in the synthesis of anacardic acids.[38] So, oxazoline **3** was treated at room temperature with the Grignard reagent **4b**—freshly prepared from Mg and α-bromostyrene—yielding the 1,1-diphenylethene derivative **5** (90%).[39]

The 1,6-conjugated addition of lithium amide from *N*-benzylamine to oxazoline **5** was carried out under standard conditions for the hydroamination of *o*-vinylphenyloxazolines (−55 °C, THF, 2 h)[32] leading to compound **6** as expected, but in low yield. An enhancement of the reactivity was achieved by performing the reaction at room temperature leading to **6** in 63% yield.[40] This experimental observation can be rationalized because of steric hindrance of phenyl moiety in the double bond. The compound without phenyl group has the double bond coplanar with the oxazoline ring in the minimal energy conformation (Fig. 2a). However that is not possible for compound **5** (Fig. 2b).[41] Consequently, it seems reasonable that the reaction requires higher temperatures as compared with coplanar *o*-vinylphenyloxazolines.[32] It is noteworthy that the addition of lithium amide takes place at room temperature, although it is generally reported that the addition of organometallic reagents must be carried out below −20 °C to avoid its addition to the C=N bond of the oxazoline ring.[36]

The subsequent steps of the synthesis of 4-phenyl-tetrahydroisoquinoline **1a** are straightforward. Oxazoline **6** is converted into ester **7** (60% yield)[42] by removing the oxazoline group in acidic conditions. The nitrogen ring formation is achieved by a simple two-step procedure (hydrogenolysis of the N-benzylic bond of **7** with Pd–C followed by the treatment of the crude product with sodium acetate at 50 °C), giving amide **8** (80% combined yield).[43] Finally, the reduction of the amide group to amine is performed with $LiAlH_4$, yielding the 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) (92%),[44,45] showing identical spectral data as those previously reported.[46]

In conclusion, a simple and efficient method for the synthesis of 2-methyl-4-phenyltetrahydroisoquinoline from 2-methoxybenzoic acid (21% overall yield) following a linear sequence of six chemical operations is reported. This paper also provides an additional demonstration of the utility of the 1,6-conjugate additions of nitrogen nucleophiles developed in our group.[32–34,47] The methodology represents a general tool for the synthesis of 4-aryl-tetrahydroisoquinolines.

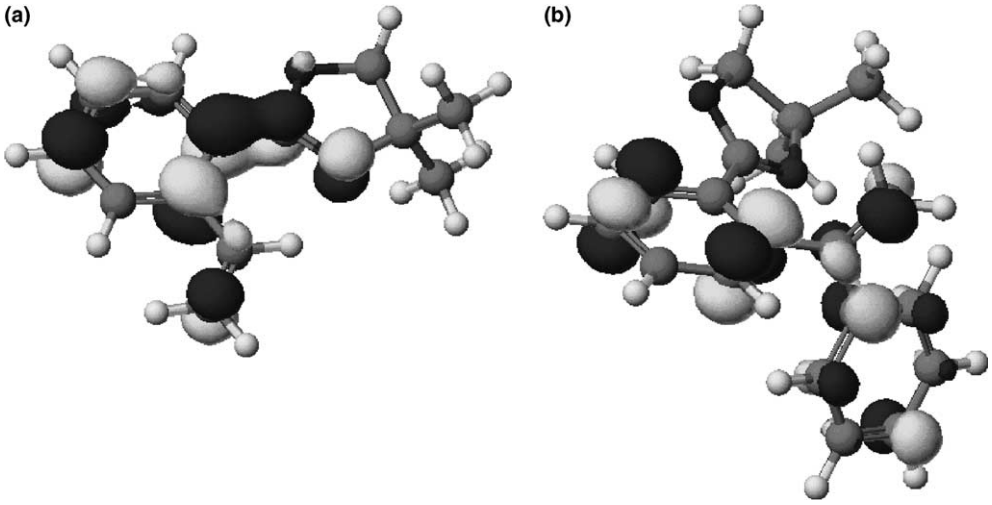

Figure 2. (a) LUMO of 4,4-dimethyl-2-(2-vinylphenyl)-2-oxazoline, $E = -0.543$ eV; (b) LUMO+1 of 4,4-dimethyl-2-[2-(1-phenylvinyl)phenyl]-2-oxazoline (**5**), $E = +0.130$ eV.[41]

Acknowledgements

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39. Experimental procedure for compound **5**. Freshly prepared Grignard reagent **4b**—by refluxing α-bromostyrene (6.26 g, 34.2 mmol), Mg (1.56 g, 64.2 mmol) and 1,2-dibromoethane (462 mg, 2.46 mmol) in THF for 2 h—was added to a solution of 2-methoxy-2-phenyl-4,4-dimethyl-2-oxazoline **3** (3.36 g, 16.4 mmol) in dry THF (30 ml) at room temperature. After being stirred for 16 h, the mixture was partitioned between satd. aq. NH_4Cl and ether. The ether extract was dried, concentrated and purified by column chromatography (SiO_2, AcOEt/hexane, 3:7), giving **5** (4.07 g, 90%) as a pale yellow oil.
40. Experimental procedure for compound **6**. 2-Oxazoline **5** (306 mg, 1.11 mmol) in dry THF (15 ml) was added dropwise to a solution of lithium amide, prepared by the addition of *n*-BuLi (1.97 ml, 3.15 mmol, 1.6 M in hexanes) to a solution of N-methylbenzylamine (381 mg, 3.15 mmol), in dry THF at 0 °C for 30 min. The reaction was allowed to warm to room temperature and left for 24 h. The reaction mixture was quenched with MeOH, and partitioned between 10% aq NaOH and ether. The ether extract was dried, evaporated and purified by column chromatography (SiO_2, AcOEt/hexane, 3:7), giving compound **5** (279 mg, 63%) as a colorless oil.
41. In fact, the LUMO energy of the compound without phenyl substituent is lower than that of LUMO+1 for compound with the phenyl group. The addition must take place at LUMO+1, in order to have the appropriate orbital coefficients with lobes on the vinyl group. Orbitals were modeled by Fujitsu, CAChe Pro, version 6.1, based on PM3 Hamiltonian.
42. Experimental procedure for compound **7**. 20% aq H_2SO_4 (20 ml) in absolute EtOH was added to a solution of compound **6** (162 mg, 0.41 mmol) at room temperature. After refluxing for 24 h, the solvent was evaporated and the resulting residue was partitioned between ether and satd aq $NaHCO_3$. The aqueous layer was extracted with ether, and the combined ether extracts were dried, concentrated and purified by column chromatography (SiO_2, AcOEt/hexane, 3:7) giving **7** (91 mg, 60%) as a yellow oil.
43. Experimental procedure for compound **8**. A solution of compound **7** (67 mg, 0.18 mmol) in AcOH/EtOH (1:9, 10 ml) in presence of Pd–C (15 mg) was hydrogenated at 50 psi for 12 h. The reaction mixture was filtrated through Celite, and concentrated. The resulting residue was dissolved in a solution of sodium acetate (20 mg, 0.24 mmol) in abs. EtOH (10 ml) and heated at 50 °C for 12 h. The solvent was evaporated and the residue purified by column chromatography (SiO_2, AcOEt/hexane, 3:7), giving compound **8** (34 mg, 80% yield) as a white solid.
44. Experimental procedure for 2-methyl-4-phenyltetrahydroisoquinoline (**1a**). A solution of compound **8** (66 mg, 0.28 mmol) in THF (10 ml) was added to a suspension of $LiAlH_4$ (22 mg, 0.59 mmol) in THF (5 ml) at room temperature, and then was refluxed for 2 h. The reaction was worked up by sequential addition of water (0.5 ml), aq 10% NaOH (1 ml) and water (0.5 ml). The organic layer was dried, evaporated and purified by column chromatography, (SiO_2, AcOEt/hexane, 4:6), giving 2-methyl-4-phenyltetrahydroisoquinoline (**1a**) (57 mg, 92%) as a viscous oil.
45. All the new compounds exhibit satisfactory spectral data. Selected spectral data. Compound **6**: IR (KBr film): 1650 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 1.35 (s, 3H, Me), 1.40 (s, 3H, Me), 2.30 (s, 3H, NMe), 2.90–3.02 (m, 2H, CH_2CHPh), 3.55 (d, 1H, PhCH_2NMe, $J = 13.2$ Hz), 3.61 (d, 1H, PhCH_2NMe, $J = 13.3$ Hz), 4.09 (s, 2H, CH_2O), 5.60 (t, 1H, $J = 7.8$ Hz, CH_2CHPh), 7.17–7.36 (m, 13H, ArH), 7.74 (d, 1H, $J = 6.7$ Hz, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): 28.5 (NMe), 42.4, 43.3 (C(CH_3)$_2$), 62.1 (PhCH_2NMe), 62.6 (CH_2CHPh), 67.9 (C(CH_3)$_2$), 78.6 (CH_2O), 125.8, 126.0, 126.8, 127.9, 128.1, 128.7, 128.8, 129.1, 130.0, 130.4, 139.3, 143.6 and 143.7 (Ar), 162.6 (C=N). MS *m/z* (EI): 398 (M^+, 1), 134 (100), 91 (62). $C_{27}H_{30}N_2O$ calcd. (%): C, 81.37; H, 7.59; N, 7.03, found C, 81.41; H, 8.08; N, 7.04. Compound **8**: mp 95.6–97.3 °C (hexane) (lit.[48] 79–80 °C). IR (KBr): 1642 (CON) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 3.10 (s, 3H, NMe), 3.71 (dd, 1H, $J = 8.0$, 12.4 Hz, CH_2CHPh), 3.81 (dd, 1H, $J = 5.2$, 12.4 Hz, CH_2CHPh), 4.33 (dd, 1H, $J = 5.2$, 8.0 Hz, CH_2CHPh), 6.90 (m, 1H, ArH), 7.18 (m, 2H, ArH), 7.30–7.39 (m, 5H, ArH), 8.19 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): 35.3 (NMe), 43.9 (CH_2CHPh), 55.0 (CH_2CHPh), 121.1, 127.3, 127.4, 128.2, 128.4, 128.8, 129.4, 131.8, 140.6 and 140.7 (Ar), 164.6 (C=O). MS (EI): 238 (M^++1, 7), 237 (M^+, 34), 194 (100). $C_{16}H_{15}NO$ calcd. (%): C, 80.98; H, 6.37; N, 5.90, found C, 80.53; H, 6.60; N: 5.93.
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