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A new synthesis of 3-alkyl-1-isoindolinones

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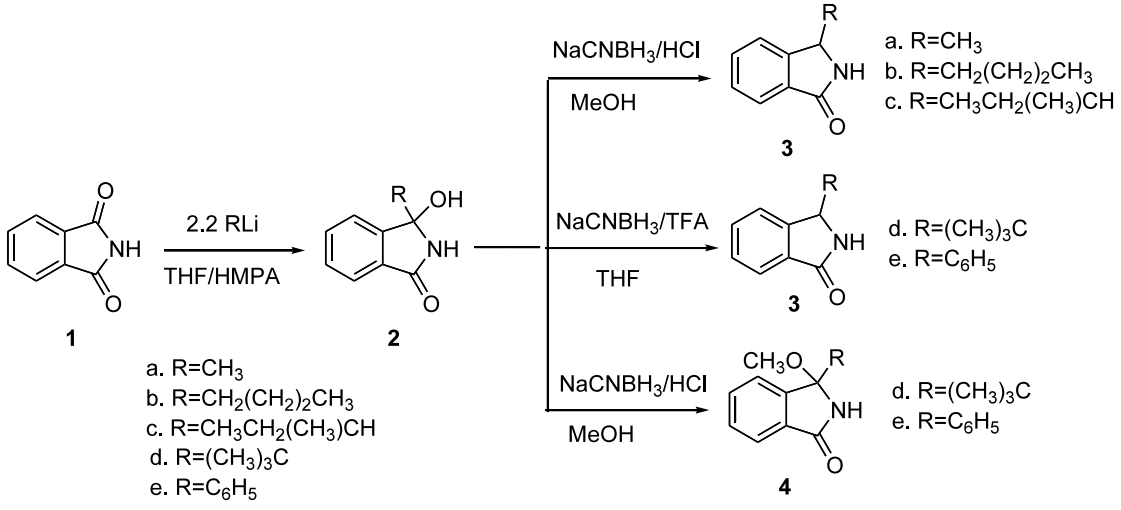
Abstract—A new, concise, and efficient method for the synthesis of 3-alkyl-1-isoindolinones was described. 3-Alkyl-3-hydroxy-2,3-dihydro-1-isoindolinones, prepared from the reaction of phthalimide and alkyl lithium, were treated with sodium cyanoborohydride in acidic medium to concomitantly undergo dehydration and reduction leading to various 3-alkyl-1-isoindolinones in good yields.

3-Alkyl-1-isoindolinone, a structural unit or key intermediate of naturally occurring alkaloids or synthetic compounds, attracts both synthetic and natural product chemists for its various biological activities. Just as bisquaternary bisphthalimidine derivatives have a potential allosteric activity;[1] pazinaclone exhibits anxiolytic and anticonvulsant activities;[2] *p*-MPPI analogs display a very high binding affinity for 5-HT_{1A} receptors in vitro;[3] indocarbazoles exhibit a protein kinase activity;[4] and (*R*)-(+)-9b-phenyl-2,3-dihydrothiazolo-[2,3-*a*]isoindol-5-(9b*H*)-one exhibits an activity for anti HIV-1 reverse transcriptase.[5] However, the strategies for the construction of 3-alkyl-1-isoindolinones are quite insufficient. Some methods that were recently reported include: (i) palladium-catalyzed reaction of 2-iodobenzamide with trimethylsilylacetylene, followed by cyclization with acid chloride or acetic anhydride, and finally by catalytic hydrogenation;[6] (ii) condensation of phenylglycinol with the corresponding ketoacid, followed by ring opening with Lewis acid and triethylsilane;[7] and more recently (iii) sequential metalation, and multi-step *C*,*N*-deprotection from 3-benzotriazolyl-2-dimethylamionophthalimidine, reported by Deniau et al.[8] Even though some drawbacks, such as tedious reaction conditions, commercially unavailable starting materials, multiple reaction steps, and low yields, still exist, the development of a more concise and efficient method is requisite.



Scheme 1.

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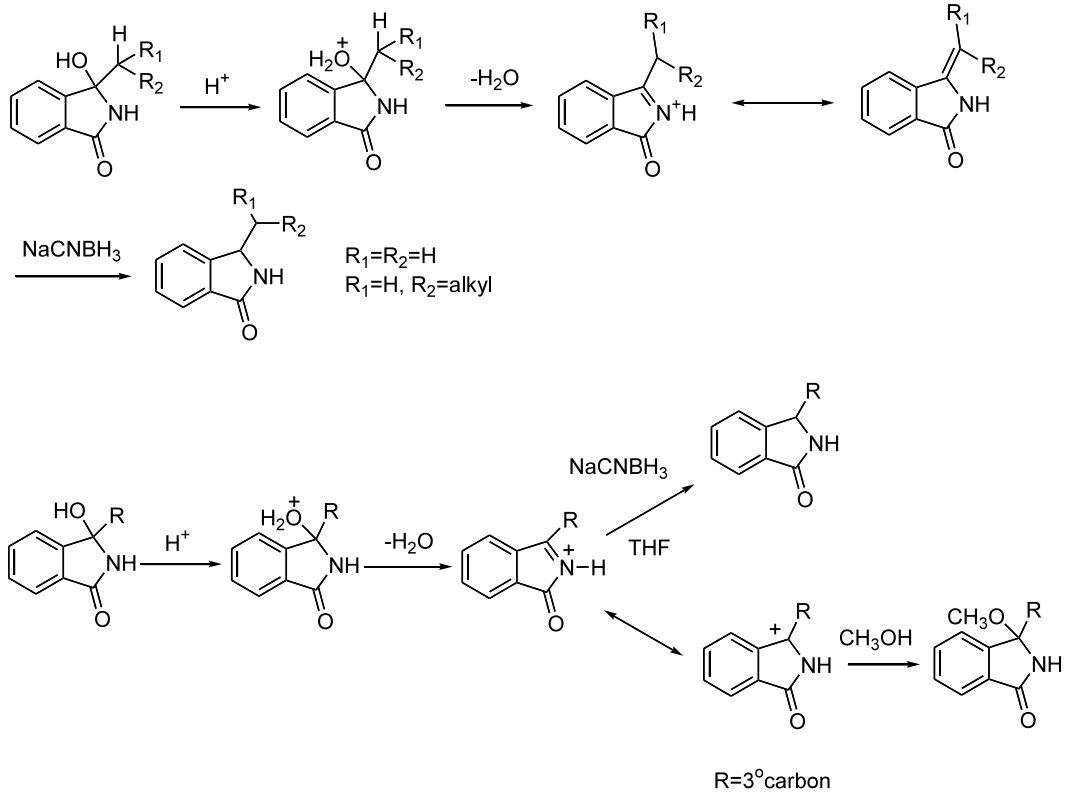
Herein, we disclose a novel, concise, and efficient method, starting from commercially available and inexpensive phthalimide, for the synthesis of various 3-alkyl-1-isoindolinones in two steps and in high overall yields (Scheme 1).

When phthalimide (**1**) was treated with various alkyl lithiums (2.2 equiv.) in THF/HMPA (4/1), it furnished 3-alkyl-3-hydroxy-2,3-dihydroisoindol-1-ones (**2a–e**) in yields of 75–78%, respectively. Subsequently, compounds **2a–c** were dehydrated, and reduced concomitantly by sodium cyanoborohydride in the presence of HCl in methanol, to afford 3-alkyl-1-isoindolinones (**3a–c**) in yields of 92–94%, respectively. On the other hand, when compounds **2d–e** were dehydrated and reduced concomitantly by sodium cyanoborohydride in the presence of THF in TFA, they afforded 3-alkyl-1-isoindolinones (**3d–e**) in yields of 92–94%, respectively. Under the same conditions as those used for the preparation of **3a–c**, **2d–e** gave 3-alkyl-3-methoxy-2,3-dihydroisoindol-1-ones (**4d–e**) instead. From the above experimental results and previous studies,[9] it can be stated that the primary or secondary alkyl group at the 3-position in compounds **2a–c** dehydrated easily into the *N*-acyliminium ion, which stabilized and coexisted with the benzylidene molecule by resonance in an acidic medium, and was then reduced by the hydride donor ($NaCNBH_3$ in methanol) to give **3a–b**. Under the same conditions, the tertiary alkyl group at the 3-position of **2d–e** underwent dehydration in HCl leading a stable acyliminium ion, by resonance with benzylic carbocation, and was then attacked by the solvent (methanol) to give **4d–e**. If an aprotic solvent was present, such as in THF in TFA, the forming acyliminium ion was subsequently reduced by $NaCNBH_3$ to furnish the desired compounds **3d–e**, respectively. A proposed reaction mechanism for this reaction is presented in Scheme 2.

In conclusion, a new and concise two-step method for the preparation of various 3-alkyl-1-isoindolinones from phthalimide through alkylation, dehydration, and with concomitant reduction by sodium cyanoborohydrate in acidic media, was established in good yields.

General procedure for the preparation of 3-alkyl-3-hydroxy-2,3-dihydroisoindol-1-ones (2a–e)

Under dry N_2, phthalimide (2.94 g, 20 mmol) dissolved in anhydrous THF (24 mL) and HMPA (8 mL) was stirred at room temperature to give a clear solution. The solution was cooled to −40°C in an immersion cooler, then alkyl lithium (14 mL, 21 mmol) was added dropwise, and the solution was stirred at −40°C for 1 h. To the cooled solution was added additional alkyl lithium (14 mL, 21 mmol), and this mixture was then stirred at −40°C for 9 h. After warming the solution to room temperature, it was carefully quenched with saturated NH_4Cl (5 mL). After removing the THF with a rotavapor in vacuo, the residue was purified under vacuum, removing HMPA with a Kugelrohr apparatus, to give a crude solid. This was purified by a silica gel



Scheme 2.

chromatographic column (ethyl acetate/*n*-hexane = 1/1) to give pure, colorless crystals of **2a** (77%),[10] **2b** (75%),[11] **2c** (77%),[12] **2d** (76%),[13] and **2e** (78%),[11] respectively.

Selected spectral data for ***2d***: Colorless crystal; mp 190–191°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 9H, CMe_3), 3.86 (br s, 1H, OH), 7.23 (br s, 1H, NH), 7.33 (td, J = 7.6, 1.0 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.50 (td, J = 7.6, 1.0 Hz, 2H), 7.60 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.19, 38.60, 92.46 (COH), 123.35, 123.60, 129.22, 131.27, 132.05, 147.98, 169.60 (C=O). Anal calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.93; H, 7.56; N, 6.69%.

General procedure for the preparation of 3-alkyl-2,3-dihydroisoindol-1-ones (3a–e)

Procedure for ***3a–c***: Under nitrogen, 3-alkyl-2,3-dihydroisoindol-1-ones (**3a–c**) (12 mmol) dissolved in MeOH (30 mL) were stirred at room temperature, and then added portionwise to $NaCNBH_3$ (0.84 g, 13.4 mmol), followed by concd HCl (5–6 drops). The reaction mixture was allowed to stir at ambient temperature for 2 h, and then concentrated in vacuo. The residue was in partition with ethyl acetate (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×25 mL). The organic layers were combined, washed with brine (2×25 mL), dried with anhydrous K_2CO_3, and then filtered. The filtration was concentrated in vacuo, and the resulting residue was purified with silica gel chromatographic column (ethyl acetate/*n*-hexane = 1/1) to give pure **3a** (94%),[8] **3b** (92%),[8] and **3c** (93%), respectively.

Procedure for ***3d–e***: The procedure was the same as for **3a–c**, but the solvent (THF) and the acidic medium (TFA) were used instead to give **3d** (83%),[8] and **3e** (85%),[8] respectively.

Selected spectral data for ***3b*** (2.12 g, 77%): Colorless crystals; mp 88–89°C (ethyl acetate/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.1 Hz, 3H, Me), 1.29–1.37 (m, 3H), 1.43–1.47 (m, 1H), 1.64–1.66 (m, 1H), 1.91–1.96 (m, 1H), 4.62 (dd, J = 7.4, 4.7 Hz, ArC*H*), 7.42 (d, J = 7.3 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.54 (td, J = 7.5, 1.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 8.17 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.80 (Me), 22.55, 27.49, 34.18 (CH_2), 57.06 (NCH), 122.33, 123.59, 127.88, 131.59, 132.05, 147.80 (Ar-C), 171.39 (C=O); MS (EI, 70 eV), m/z 189 (M^+, 11.34), 132 (100), 104 (14). Anal calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.18; H, 8.01; N, 7.43%.

Procedure for **2d–e**: Using a similar procedure as for the preparation of **3a–c**, methanol in the presence of concd HCl (as solvent) gave **4d–e**.

Selected spectral data for ***4e*** (60%):[14] Colorless crystals; mp 136°C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (s, 3H, OMe), 7.26–7.34 (m, 4H), 7.43–7.56 (m, 5H), 7.82 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.25 (OMe), 92.17, 123.05, 123.60, 125.46, 128.42, 128.45, 129.48, 131.06, 132.74, 139.83, 146.48, 170.02 (C=O).

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