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Conversion of Phthalimides to Isoindolines by Diborane

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Summary. Reduction of *N*-alkylsubstituted phthalimides to the corresponding isoindolines by means of diborane is herein described.

Keywords. Reduction; Hydrides; Heterocycles.

Introduction

Reduction of amides to the corresponding amines has been examined with a variety of metal hydrides. Most of them are extremely powerful reducing agents capable of reducing almost all the functional groups in an organic molecule [1].

Reduction of phthalimides has been explored with a limited number of metal hydrides showing that the compound obtained depends on the type of reducing agent employed in the reaction. Thus, *N*-benzylphthalimide has been reduced with lithium aluminum hydride (*LAH*) to give essentially *N*-benzylisoindoline and only trace amounts of the corresponding isoindole [2]. Replacement of *LAH* for sodium bis-(2-methoxyethoxy)aluminum hydride (*SDMA*) resulted in the formation of the substituted *N*-benzylisoindole in a 60% yield [2]. Also *N*-4-pentenylisoindole has been prepared in *ca.* 70% yield by reduction of *N*-4-pentenylphthalimide with *SDMA* [3]. When *N*-benzyl-3-nitrophthalimide was reduced with a large excess of sodium borohydride in methanol, the resulting ω-carbinol lactam was isolated in a 94% yield as a mixture of positional isomers (65/35) after a 20 minutes to 1 hour period of the reaction. This ratio and regioselectivity depends on the reaction temperature [4].

Particularly, diborane proved to be a mild and selective agent allowing the presence of many other substituents less susceptible to the reducing action of the reagent [1, 5–7]. Besides, diborane has been successfully utilized for reduction of

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halogen-substituted amide derivatives to the corresponding halosubstituted amines giving excellent yields [1].

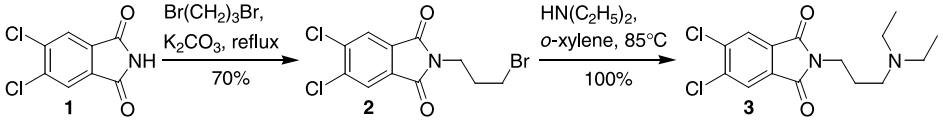
We herein report our results involving the reduction of substituted phthalimides to the corresponding isoindolines by employing diborane.

Results and Discussion

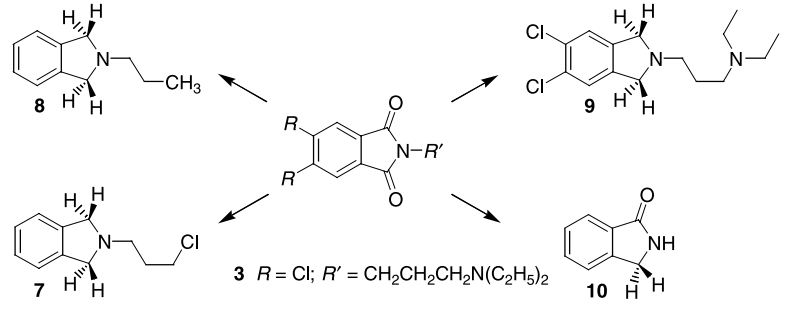
The required substituted phthalimides **4** and **5** were prepared by alkylation of the unsubstituted precursor **6**, according to *Samejima et al.* [8]. Compound **2** was conveniently synthesized by a base catalyzed alkylation of 4,5-dichlorophthalimide (**1**) with 1,3-dibromopropane at reflux temperature (70% yield). The treatment of *N*-(3-bromopropyl)-4,5-dichlorophtalimide (**2**) with an excess of *N*,*N*-diethylamine in *o*-xylene led to substituted phthalimide **3** in quantitative yields (Scheme 1).

N-(3-Chloropropyl)isoindoline (**7**) was obtained in a 90% yield by reduction of *N*-(3-chloropropyl)phthalimide (**4**) employing diborane in *THF* at room temperature for 72 hours. Under the same conditions, *N*-(3-bromopropyl)phthalimide (**5**) afforded *N*-propylisoindoline (**8**) due to hydrogenolysis of the halide since bromine is more reactive than chlorine in nucleophilic substitution reactions. The substituted phthalimide **3** was also successfully converted to the corresponding isoindoline **9** in a 90% yield. However, **9** proved to be unstable and to undergo extensive decomposition by atmospheric exposure even at low temperature. When reduction was achieved on the unsubstituted phthalimide **6**, 2,3-dihydro-*1H*-isoindol-1-one (**10**) was obtained as the main product (Scheme 2).

The ^{1}H NMR spectra of the *N*-substituted isoindolines **7**, **8**, and **9** showed two non-equivalent doublets at $\delta = 4.5$ and 4.2 ppm with a characteristic *gem*-coupling



Scheme 1



Scheme 2

constant of $J = 14$ Hz which can be assigned to the pyrrolidine ring. On the contrary, both hydrogens appear as only one singlet at $\delta = 4.5$ ppm in the spectrum of isoindolinone **10**.

The reduction of the phthalimide rings was evidenced in the IR spectra on account of the disappearance of the corresponding NC=O stretching signals around $\bar{\nu} = 1780$ and 1715 cm^{-1}. In the case of isoindolinone **10**, a typical lactam band was observed at 1682 cm^{-1}. Mass spectra of **7**, **8**, and **10** are in good agreement with the structures proposed. However, the instability of **9** did not allow either mass spectrum or recrystallization.

In conclusion, the reduction of *N*-substituted phthalimides by means of diborane is an useful method to directly produce *N*-substituted isoindolines in excellent yields.

Experimental

Melting points were determined on an Electrothermal 9100 capillary melting point apparatus. ^{1}H NMR was recorded on a Bruker MSL 300 spectrometer. Mass spectra were obtained with a TRIO 2 (electronic ionization 70 eV) spectrometer. Infrared spectra were carried out with a Perkin Elmer Spectrum One FT-IR spectrometer. Elemental analyses (C, H, N) were conducted using the Elemental Analyzer Carlo Erba EA 1108; their results were found to be in good agreement (±0.2%) with calculated values. Chromatography columns were prepared with TLC Kiesegel (Merck). 4,5-Dichlorophthalimide (**1**) was synthesized according to *Wöhrle et al.* [9]. Reagents were purchased from Sigma-Aldrich.

N-(3-Bromopropyl)-4,5-dichlorophthalimide (**2**, $C_{11}H_8BrCl_2NO_2$)
A mixture of 5.2 g **1** (24 mmol), 25 cm^3 1,3-dibromopropane (245 mmol), and 2 g anhydrous K_2CO_3 (14.5 mmol) was stirred and heated at reflux for 3 h, then poured into 150 cm^3 H_2O, and extracted with 3×70 cm^3 CH_2Cl_2. The combined extracts were then washed with 3×70 cm^3 H_2O, dried (Na_2SO_4), and evaporated in vacuum. The solid residue was dissolved in a small volume of CH_2Cl_2 and filtered through a silica-gel column, packed and pre-washed with the same solvent. After evaporation of the solvent, the solid residue was recrystallized from *Et*OH to give 5.6 g (70%) **2**. Mp 134–135°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.93$ (s, 2H-Ar), 3.83 (t, $J = 6.9$ Hz, NCH_2), 3.40 (t, $J = 6.7$ Hz, CH_2Br), 2.25 (m, $NCH_2CH_2CH_2Br$) ppm; IR (KBr): $\bar{\nu} = 1779$, 1716 (NC=O phthalimide) cm^{-1}.

N-[3-(N,N-Diethylamino)propyl]-4,5-dichlorophthalimide (**3**, $C_{15}H_{18}Cl_2N_2O_2$)
A mixture of 0.27 g **2** (0.8 mmol) and 0.4 cm^3 *N*,*N*-diethylamine (4 mmol) in 0.6 cm^3 anhydrous *o*-xylene was heated at 85°C for 10 h. After evaporation to dryness in vacuum, the solid residue was dissolved in a small volume of CH_2Cl_2:*Me*OH (9:1), and filtered through a silica-gel column, packed

Table 1. Elemental analyses

Compound	Calculated			Found		
	C (%)	H (%)	N (%)	C (%)	H (%)	N (%)
2, $C_{11}H_8BrCl_2NO_2$	39.20	2.39	4.16	39.30	2.20	4.20
3, $C_{15}H_{18}Cl_2N_2O_2$	54.72	5.51	8.51	54.60	5.40	8.60
7, $C_{11}H_{14}ClN$	67.51	7.21	7.16	67.62	7.11	7.06
8, $C_{11}H_{15}N$	81.94	9.38	8.69	81.80	9.40	8.73
9, $C_{15}H_{22}Cl_2N_2$	59.80	7.36	9.30	59.59	7.15	9.15

and pre-washed with the same solvent. After evaporation of the solvent, a highly hygroscopic white solid was obtained, 0.265 g (quantitative yields) **3**. Mp 230°C (dec); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.92$ (s, 2H-Ar), 3.78 (t, $J = 6.8$ Hz, $NCH_2(CH_2)_2N(C_2H_5)_2$), 2.97 (m, $CH_2N(CH_2CH_3)_2$), 2.18 (m, $NCH_2CH_2CH_2N$), 1.29 (t, $J = 7.2$ Hz, $CH_2N(CH_2CH_3)_2$) ppm; IR (KBr): $\bar{\nu} = 1779$, 1716 (NC=O phthalimide) cm^{-1}.

N-(3-Chloropropyl)isoindoline (**7**, $C_{11}H_{14}ClN$)
Diborane from boron trifluoride etherate (5 cm^3) – slowly dropped into a suspension of 1.5 g sodium borohydride in 5 cm^3 diglyme – was bubbled into a suspension of 0.5 g **4** (2.3 mmol) in 60 cm^3 dry *THF*. The mixture was stirred for 72 h at room temperature and the excess diborane was decomposed by addition of 0.1 *N* HCl until *pH* 2 was reached, and stirred for an additional 2 h period. 1 *N* NaOH was added until *pH* 10 was reached and the solution was then extracted with 3×30 cm^3 CH_2Cl_2. The combined extracts were washed with 3×30 cm^3 H_2O, dried (Na_2SO_4), and evaporated in vacuum. The solid residue was dissolved in a small volume of CH_2Cl_2 and filtered through a silica-gel column, packed and pre-washed with the same solvent. After evaporation of the solvent, the solid residue was recrystallized from CH_2Cl_2:*n*-hexane to give 0.394 g (90%) **7**. Mp 79–81°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.28$ (m, 2H-Ar), 7.22 (m, 2H-Ar), 4.56 (d, $J = 14$ Hz, $Ar(CHH)_2N$), 4.19 (d, $J = 14$ Hz, $Ar(CHH)_2N$), 3.58 (t, $J = 6.0$ Hz, CH_2Cl), 3.16 (t, $J = 8.0$ Hz, NCH_2), 2.29 (m, $NCH_2CH_2CH_2Cl$) ppm; IR (KBr): no phthalimide signal was observed; MS (70 eV): m/z (%) = 196 (4.10, $M^+ + 1$), 195 (3.05, M^+), 194 (11.83, M^+-1), 132 (46.81), 118 (44.54), 105 (100).

N-Propylisoindoline (**8**, $C_{11}H_{15}N$)
Reduction of 0.5 g **5** (1.87 mmol) using the same procedure described for **7** afforded after recrystallyzation from *Me*OH-H_2O 0.2 g (67%) **8**. Mp 66–69°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.27$ (m, 2H-Ar), 7.18 (m, 2H-Ar), 4.53 (d, $J = 14$ Hz, $Ar(CHH)_2N$), 4.17 (d, $J = 14$ Hz, $Ar(CHH)_2N$), 2.94 (t, $J = 8.5$ Hz, NCH_2), 1.72 (m, $NCH_2CH_2CH_3$), 0.88 (t, $J = 7.4$ Hz, CH_3) ppm; IR (KBr): no phthalimide signal was observed; MS (70 eV): m/z (%) = 160 (21.06, M^+), 132 (50.25), 118 (12.28), 105 (100).

*N-[3-(N,N-Diethylamino)propyl]-4,5-dichloroisoindoline (***9**, $C_{15}H_{22}Cl_2N_2$)
Reduction of 0.4 g **3** (1.2 mmol) using the same procedure described for **7** afforded after purification by filtering through a silica-gel column, packed and pre-washed with CH_2Cl_2:*Me*OH (99.5:0.5), 0.33 g (90%) **9**. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.32$ (s, 2H-Ar), 4.45 (d, $J = 14$ Hz, $Ar(CHH)_2N$), 4.15 (d, $J = 14$ Hz, $Ar(CHH)_2N$), 2.97 (t, $J = 8.0$ Hz, $NCH_2(CH_2)_2N(C_2H_5)_2$), 2.84 (q, $J = 7.4$ Hz, $CH_2N(CH_2CH_3)_2$), 2.64 (t, $J = 8.2$ Hz, $CH_2N(C_2H_5)_2$), 2.28 (m, $NCH_2CH_2CH_2N$), 1.19 (t, $J = 7.4$ Hz, $CH_2N(CH_2CH_3)_2$) ppm.

2,3-Dihydro-1H-isoindol-1-one (**10**, C_8H_7NO)
Reduction of 0.1 g **6** (0.68 mmol) using the same procedure described for **7** afforded after purification by TLC using CH_2Cl_2:*Me*OH (9:1), $Rf = 0.6$, followed by recrystallization from CH_2Cl_2-*n*-hexane 0.032 g (35%) **10**. Mp 149–151°C (Ref. [10] 151°C); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.05$ (bs, NH), 7.87 (m, 1H-Ar), 7.57 (m, 1H-Ar), 7.48 (m, 2H-Ar), 4.47 (s, $ArCH_2N$) ppm; IR (KBr): $\bar{\nu} = 1682$ (NC=O amide) cm^{-1}; MS (70 eV): m/z (%) = 133 (100, M^+), 104 (52.82), 77 (48.87).

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