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THE THORPE-INGOLD EFFECT IN CYCLIC IMIDES. PART III

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Abstract – Reactivity of phenyllithium with a number of succinimide derivatives were studied. We have shown that the Thorpe-Ingold effect affected both the reaction products distribution and their structures. Regioselectivity of these reactions were rationalized. Structures were confirmed with NMR and crystallographic methods.

The pyrrolidine heterocyclic system forms a structural motif that is common to a diverse group of natural products.[1] Several biologically relevant alkaloids belong to this important group, mentioning for example atropine which is anticholinergic, mydriatic and stimulates respiratory system or physostigmine that is parasympathomimetic and exhibits profound anticholinergic activity.[2]

On the other hand, there are several dozens of synthetic compounds that contain a pyrrolidine nucleus that are of importance to modern organic chemistry. Suitably designed chiral ligands bearing the pyrrolidine ring have been introduced as catalysts for enantioselective reactions.[3]

Consequently, the development of general synthetic procedures for the construction of such systems represents a real challenge in the field of both natural and purely synthetic derivatives and considerable efforts have been done in this agenda.

In a variety of cases a cyclic or acyclic substituent is located at the α position of the heterocyclic ring. Among many available methods for the introduction of the desired substituent those based on nucleophilic substitution appear to be most popular.[4] The substituent is often introduced utilizing the chemistry of carbonyl group and therefore the pyrrolidine based lactams[5] and imides[6] are frequently used.

The reduction of succimides provides an access to N-acyliminium ions that readily undergo nucleophilic addition reactions allowing the introduction of the substituent at α-position. Several natural products were

synthesized using this strategy, namely xenovenine, epibatidine and elaeokanine B.[7]

Hydroxy- and ethoxy-lactams generated from imides were used in preparation of 5-substituted pyrrolidino-2-ones via 2-phenylsulphonylpyrrolidino-2-ones. Other nucleophiles have also been used for the addition at the α position in imides. There are many examples in which Grignard reagents served for preparation of 1,4-dicarbonyl compounds.[8] Also, the chemistry of samarium(II) iodide has been employed to facilitate this task.[9]

We have already gained some experience in the synthesis of 1,5-dicarbonyl compound being in a tautomeric equilibrium between the hydroxy-lactam and the keto-amide structure.[10] This equilibrium was shown to be extremely dependent on the Thorpe-Ingold effect (*gem*-dialkyl effect). Total regioselectivity in products distribution in the case of glutarimide derivatives have been observed and explained. The presented work is intended to supplement the analogous data for succimide series.

RESULTS AND DISCUSSION

During our studies on organolithium compounds addition to the imide moiety, we turned our attention into 5-membered ring succimides. Under the influence of phenyllithium in ether at –78 °, imide **1** (**Scheme 1**) afforded a single product whose structure was unclear to us until we were able to perform a crystallographic study. From **Figure 1** which presents the ORTEP diagram of product **2**, two interesting features of this reaction can be seen.

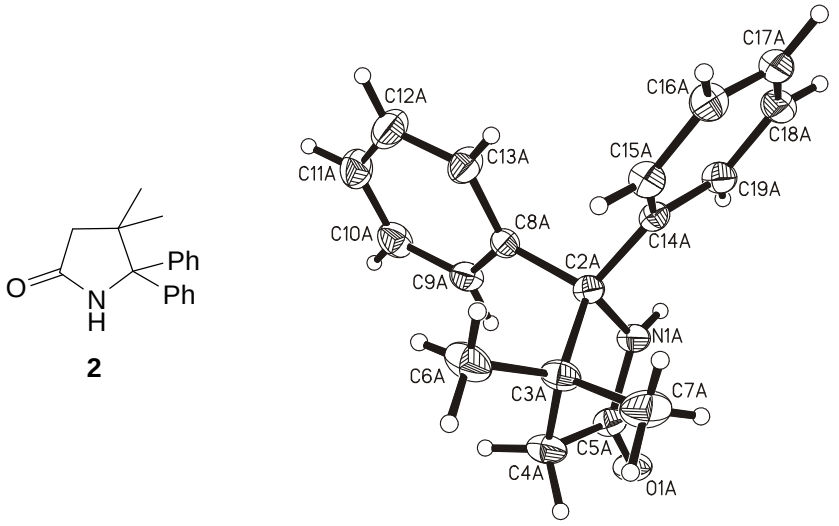
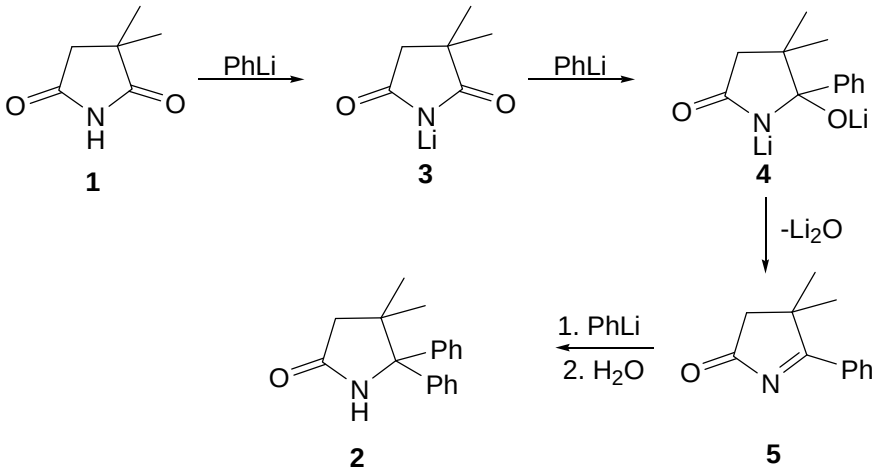


Figure 1. The structure and the ORTEP diagram of compound **2** and the numbering scheme. The non-hydrogen atoms are shown as 30% probability ellipsoids.

First, the presence of two phenyl groups needs an explanation, which might be somewhat difficult due to the absence of any by-products and/or intermediates found in the reaction mixture. In our opinion, the sequence shown in **Scheme 1** can be taken under consideration. Thus, upon addition of the first molecule of phenyllithium to the initially formed lithium salt of **1** the intermediate, compound **4** is produced. The

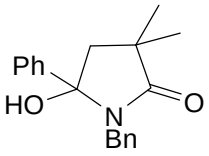
elimination of lithium oxide (Li_2O) brings about the formation of enamide **5** that in turn undergoes the addition of the second molecule of phenyllithium, affording compound **2** as a final isolated product. The process of lithium oxide elimination is not uncommon, being recently postulated by *Davis et al.*[11] to proceed under the influence of a strong base.



Scheme 1. The postulated reaction pathway for the formation of compound **2**

Other mechanism involving the open chain intermediates seems less probable.[9] Secondly, the formation of product **2** strongly suggests the remarkable regioselectivity of this addition, which proceeds at the more hindered site of the unsymmetrical molecule. This kind of interesting behaviour was observed already by Speckamp *et al.*[12] in the case of borohydride reduction of non-symmetric succimide derivatives. The observed regioselectivity was rationalized on the basis of non-equivalent interactions during the hydride anion approach to the carbonyl group. The nucleophile approaches above the less hindered carbonyl group and adds to the carbon atom at the more hindered site along a straight trajectory throughout the CO bond. Another hypothesis, in which the regioselectivity was attributed to a different electronic character of the two CO groups was shown to be non-operating. However, the latter idea might sometimes be considered as coexistent.

Since compound **1** seemed inadequate for the study on the Thorpe-Ingold effect, we decided to employ similar derivative unable to eliminate Li_2O molecule. Thus, we subjected compound **6** (**Scheme 2**) to the reaction with phenyllithium but the results that we obtained were even more surprising than in the previous case. The examination of the reaction mixture revealed the presence of four compounds. The column chromatography allowed the separation of two major compounds **7** and **8** isolated with the approx. ratio 4:1. For the major compound **7** we were able to obtain the monocrystal suitable for X-ray analysis (**Figure 2**).



7

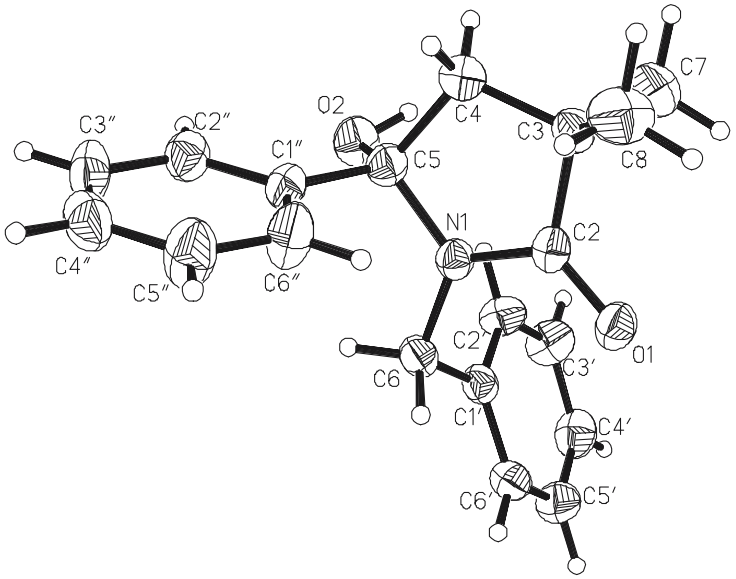


Figure 2. The structure and the ORTEP diagram of compound **7** and the numbering scheme. The non-hydrogen atoms are shown as 30% probability ellipsoids.

The structure for the oily component **8** was studied by the NOESY experiment which clearly indicated spatial arrangement of methyl groups versus OH moiety in the molecule of **8** (**Figure 3**).

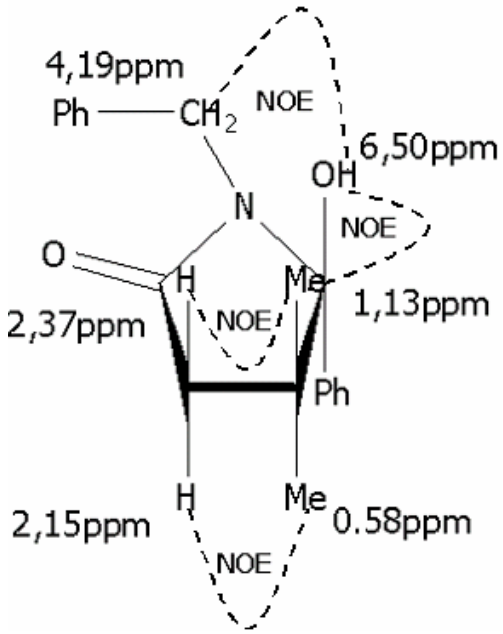
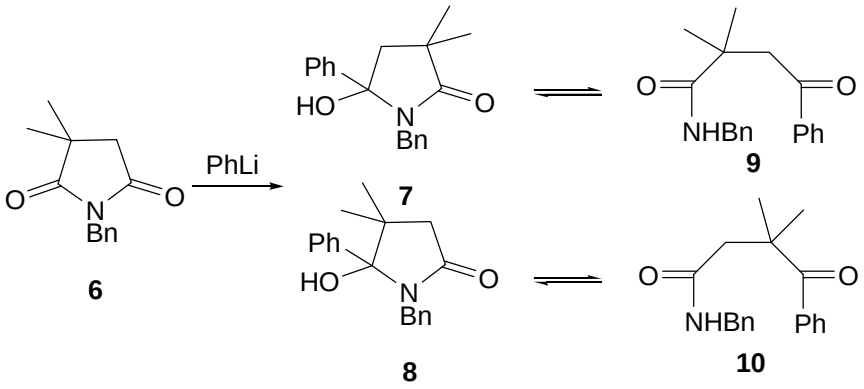


Figure 3. NOESY experiment on compound **8.**

A more detailed GC-MS analysis of the reaction mixture showed presence of two additional compounds **9** and **10**. Therefore, the final ratios of the products **7**, **8**, **9**, **10** were ca. 80:16:3:1 respectively (**Scheme 2** and **Figure 4**).



Scheme 2. The products of the reaction of imide **6** with PhLi

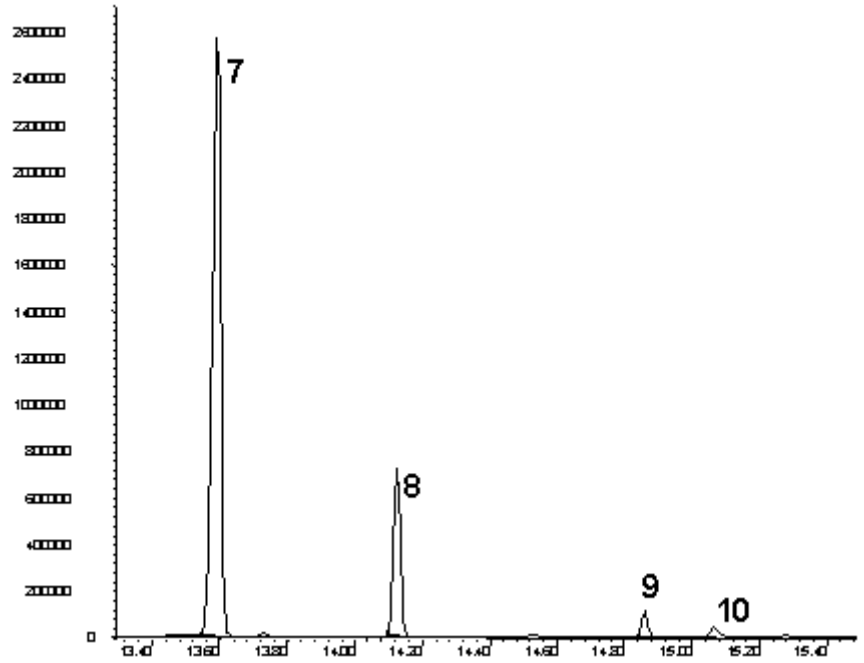


Figure 4. GC chromatogram of products formed in the reaction of imide **6** with phenyllithium.

The noticeable preference for the cyclic tautomers **7** and **8** indicates the stronger stabilization of the hydroxy-lactam system in the case of succimide derivatives, that it was observed by us in the case of glutarimide series.[10]

It is interesting to note that treating compound **8** with solvents that probably contained acidic impurities we observed their partial decomposition. Further investigation of this phenomenon showed that in fact compound **8** quantitatively forms compound **11** under the influence of TFA in CH_2Cl_2. The structure of this derivative remind unclear for us until we recorded the X-ray crystallography on it (**Figure 5**).

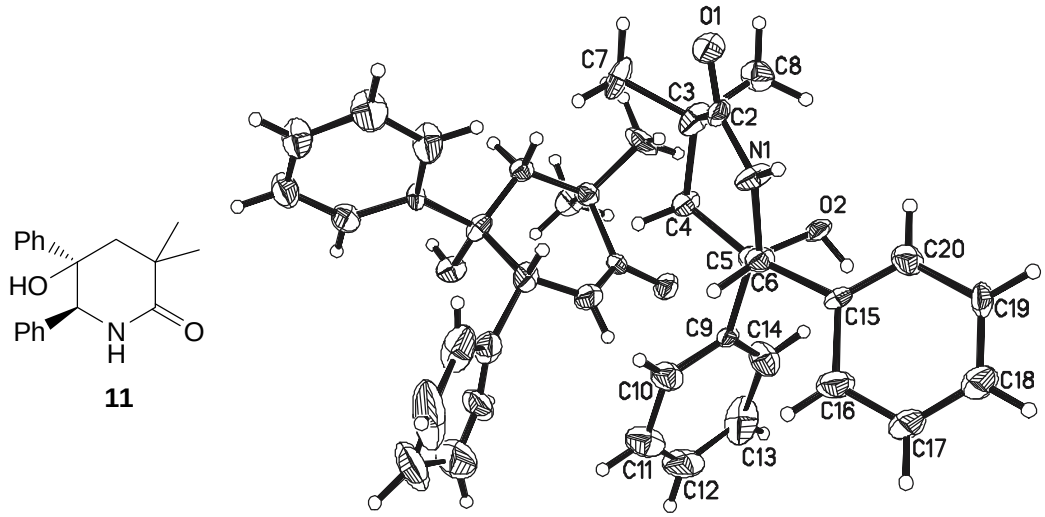


Figure 5. The structure and the ORTEP diagram of compound **11** and the numbering scheme. The non-hydrogen atoms are shown as 30% probability ellipsoids.

At this point we can not offer any reasonable mechanism rationalizing the observed rearrangement that apparently involved the 1,3-phenyl shift together with benzyl group migration.

The introduction of another pair of methyl groups in the imide framework resulted in the considerable change in the tautomeric equilibrium governed probably by the Thorpe-Ingold effect. Thus, when imide **12** (**Figure 6**) was treated with phenyllithium at –78 ºC, a single compound was the only product detected.

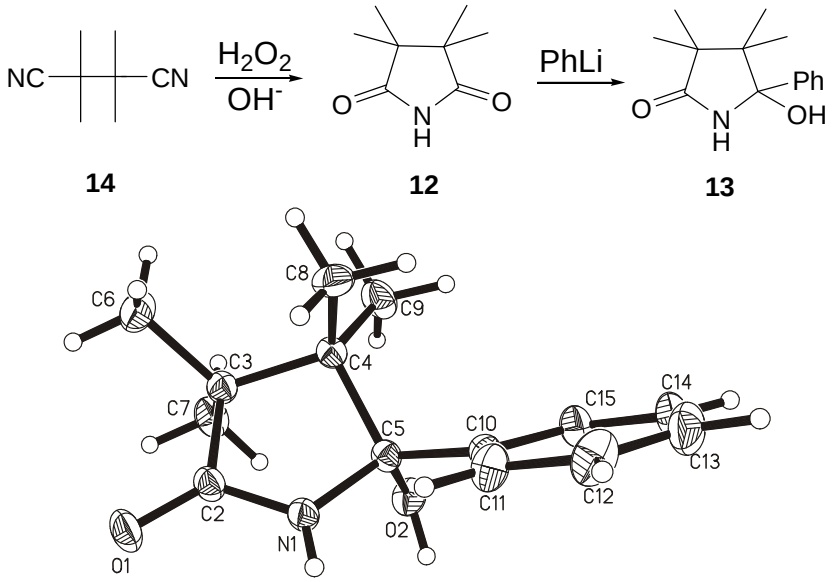


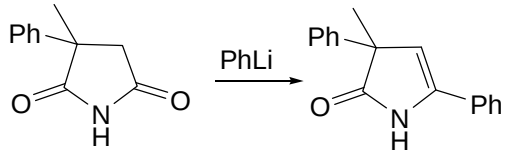
Figure 6. Reaction scheme for reaction and the ORTEP diagram for compound **13**. The non-hydrogen atoms are shown as 20% probability ellipsoids.

In ^{1}H NMR spectrum the presence of four methyl resonances (at 0.43, 0.94, 1.09 and 1.37 ppm) confirmed the cyclic structure of this compound. Also, in ^{13}C NMR spectrum a signal at 91.9 ppm was found, which was indicative of a tertiary alcohol. The absence of the *ortho* deshielding effect in ^{1}H NMR

together with the lack of carbonyl carbon atom resonance at 200 ppm in ^{13}C NMR spectrum strongly indicated a cyclic structure of this compound. The final proof for the structure of **13** came from X-ray crystallography (**Figure 6**). The result described above is in full accordance with our previous findings of a remarkable role of the Thorpe-Ingold effect on the structure of related compounds.[10]

Interestingly this effect also influenced the reactivity of selected intermediates during imide **12** synthesis. Thus, when we found dinitrile **14** somewhat difficult to hydrolyze under classical conditions due to its volatility, we subjected **14** to the oxidative saponification procedure.[13] The desired imide **12** was obtained directly with an excellent yield. It is interesting to note that 1,2-dicyanoethane gave succinic acid under the same conditions.

Finally, we subjected imide **15** to the reaction with phenyllithium. After a standard workup we isolated compound **16** in 79% yield as the sole product (**Scheme 3**).



15 **16**

Scheme 3. Reaction of **15** with phenyllithium

GENERAL

The NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz or 200 MHz for ^{1}H NMR and 125 MHz or 50 MHz for ^{13}C NMR, respectively. Tetramethylsilane (TMS) was used as the internal standard. Chemical shifts are reported in ppm. Coupling constants (*J*) are reported in hertz. Melting points are uncorrected. Column chromatographic separations were carried out on silica gel (70-230 mesh or 230-400 mesh) and were monitored by TLC on silica gel, which were visualized by UV radiation and/or iodine vapors. Diethyl ether was distilled from CaH_2 before use. Bromobenzene and chloroform were also distilled before use. In the case of sensitive compounds solvents for chromatography were redistilled and stored over neutral aluminum oxide. X-Ray crystallographic data were collected at room temperature on a Kuma KM4 single crystal κ-axis diffractometer using MoKα radiation. The data were corrected for Lorentz and polarization effects but not for absorption. Crystal structures were solved using direct methods from SHELXS97[14] and refined by the application of the SHELXL97[15] software (**Table 1**). The GC-MS system consisted of HP 6890 Plus gas chromatograph coupled to HP 5973 mass-selective detector. A column HP-5MS 30 m x 0.25 mm I. D. with 0.25 μm film thickness was used with helium as a carrier gas with constant flow F=0.6 ml/min. The injector temperature was 250 ^{o}C. Samples (0.5-1.0 μl) were introduced in a split mode with a split ratio 50:1. The oven temperature was programmed as follows: the initial temperature was set at 90 ^{o}C, held for 1 min and ramped at 12 ^{o}C/min to 290 ^{o}C and held for 5 min.

Table 1. Crystal data and structure refinement.

Compound	**2**	**7**	**11**	**13**
Empirical formula	$C_{18}H_{19}NO$	$C_{19}H_{21}NO_2$	$C_{19}H_{21}NO_2$	$C_{14}H_{19}NO_2$
Formula weight	265.34	295.37	295.37	233.30
Temperature	293(2) K	293(2) K	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/c$	Pbca
Unit cell dimensions	a = 16.213(3) Å, b = 13.524(3) Å, c = 13.909(3) Å, β= 101.92(3)º	a = 5.845(3) Å, b = 18.285(4) Å, c = 14.917(5) Å, β= 94.14(4)º	a = 9.995(2) Å, b = 11.054(2) Å, c = 29.458(6) Å, β= 94.49(3)º	a = 8.309(6) Å b = 15.364(8) Å c = 20.567(9) Å
Volume	2984.0(10) $Å^3$	1590.1(10) $Å^3$	3244.7(11) $Å^3$	2626(3) $Å^3$
Z	8	4	8	8
Density (calculated)	1.181 Mg/m^3	1.234 Mg/m^3	1.209 Mg/m^3	1.180 Mg/m^3
Absorption coefficient	0.073 mm^{-1}	0.080 mm^{-1}	0.078 mm^{-1}	0.078 mm^{-1}
F(000)	1136	632	1264	1008
Crystal size	0.65 x 0.35 x 0.3 mm^3	1.0 x 0.25 x 0.2 mm^3	0.4 x 0.5 x 0.6 mm^3	1.1 x 0.55 x 0.15 mm^3
Data collection θ range	1.98 to 30.01º	1.76 to 24.30º	1.39 to 24.77º	1.98 to 25.01º
Index ranges	-22≤ h≤ 22, -19≤ k≤ 0, 0≤ l≤ 19	0≤ h≤ 6, 0≤ k≤ 19, -17≤ l≤ 16	-11≤ h≤ 11, 0≤ k≤ 12, 0≤ l≤ 33	-9≤ h≤ 1, -17≤ k≤ 1, -24≤ l≤ 1
Reflections collected	9035	2419	5253	2813
Independent reflections	8699 [R(int)=0.0241]	2181 [R(int)=0.0340]	5134 [R(int)=0.0403]	2139 [R(int)=0.0665]
Refinement method	Full-matrix least-squares on F^2			
Data / restraints / parameters	8699 / 0 / 369	2181 / 0 / 203	5134 / 3 / 350	2139 / 0 / 162
Goodness-of-fit	1.044	1.014	2.748	1.002
Final R indices [I>2σ(I)]	R1=0.0454, wR2=0.1374	R1=0.0411, wR2=0.1116	R1=0.1832, wR2=0.5684	R1=0.0464, wR2=0.1340
R indices (all data)	R1=0.1470, wR2=0.1757	R1=0.0998, wR2=0.1336	R1=0.2494, wR2=0.5937	R1=0.1059, wR2=0.1630
$\Delta\rho_{max}$ and $\Delta\rho_{min}$ [$e \cdot Å^{-3}$]	0.305 & -0.185	0.166 & -0.181	1.573 & -0.654	0.205 &-0.244
CSD reference number[1]	CCDC 628332	CCDC 628334	-	CCDC 628333

[1] There was relatively small amount of material for **11** and the quality of monocrystal obtained was unsatisfactory. Nevertheless, the collected diffraction data enabled us to solve the structure. There are no doubts about molecular structure of **11**, but we did not decide to deposit the resultant structural data.

GENERAL PROCEDURE FOR REACTIONS BETWEEN IMIDES AND PHENYLLITHIUM

To the lithium turnings (250 mg, 36 mmol) in 30 mL of Et_2O, bromobenzene (54 mmol) in 5 mL of Et_2O was slowly added at rt with stirring during a period of 1 h. After additional 1 h the solution was cooled down to -78 °C and an appropriate imide (3.6 mmol) suspended in 5 mL of anhydrous Et_2O was added in one portion. After 30 min of stirring at -78 °C the mixture was allowed to reach rt overnight. 5 mL of water was carefully added and the reaction mixture evaporated and extracted with EtOAc (5 x 20 mL). Combined organic layers were evaporated and the residue was chromatographed giving the following products:

4,4-Dimethyl-5,5-diphenylpyrrolidin-2-one (2)

Obtained from imide (**1**)[16] (457 mg, 3.6 mmol) and isolated by column chromatography on silica gel using cyclohexane : EtOAc (1:1 v/v) as eluent with the yield 78% (745 mg, 2.8 mmol). Recrystallized from EtOAc mp 233-234 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (s, 6H), 1.65 (s, 1H, exchangeable with D_2O), 2.40 (s, 2H), 7.27 (m, 2H), 7.35 (m, 4H), 7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.2, 44.3, 47.0, 73.0, 127.1, 127.2, 128.2, 141.9, 177.2; IR (KBr, cm^{-1}) 3440, 3200, 1690, 1370; MS (ES) $[M+H]^+$ = 266, $[M+Na]^+$ = 288; HRMS m/z calcd for $C_{18}H_{19}NONa$ 288.1364, found 288.1372.

1-Benzyl-5-hydroxy-3,3-dimethyl-5-phenylpyrrolidin-2-one (7),
1-Benzyl-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (8),
N-Benzyl-2,2-dimethyl-4-oxo-4-phenylbutyramide (9), and
N-Benzyl-3,3-dimethyl-4-oxo-4-phenylbutyramide (10)

Compound (**6**)[17] (782 mg, 3.6 mmol) was subjected to the reaction with PhLi according to the General Procedure and compounds (**7**) and (**8**) were isolated by column chromatography on silica gel using gradient cyclohexane to cyclohexane: EtOAc (1:1 v/v) as eluent: compound **7** in yield 65% (691 mg, 2.3 mmol), mp 144-146°C and compound **8** in yield 18% (191 mg, 0.6 mmol), colorless oil.

1-Benzyl-5-hydroxy-3,3-dimethyl-5-phenylpyrrolidin-2-one (7): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.13 (s, 3H), 1.28 (s, 3H), 2.24 (q_{AB} J=13.8Hz, 2H), 4.14 (q_{AB} J=15.4Hz, 2H), 6.48 (s, 1H, exchangeable with D_2O), 7.10-7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.2, 26.8, 43.4, 51.9, 89.7, 125.9, 126.2, 127.4, 127.6, 127.9, 138.4, 144.2, 179.3; MS (EI) m/z (rel intensity in %) 295 (M^+, 9), 277(10), 262 (13), 175 (19), 160(3), 147 (18), 106 (100), 91 (41), 77 (14), HRMS m/z calcd for $C_{19}H_{21}NO_2Na$ 318.1475, found 318.1468.

1-Benzyl-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (8): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.58 (s, 3H), 1.13 (s, 3H), 2.26 (q_{AB} J=16.5 Hz, 2H), 4.49 (q_{AB} J=16.6 Hz, 2H), 6.50 (s, 1H, exchangeable with

D_2O), 7.28 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.49, 25.92, 41.6, 44.0, 44.2, 96.7, 126.4, 127.0, 127.5, 127.8, 127.9, 139.0, 139.8, 174.3; MS (EI) m/z (rel intensity in %) 295 (M^+, 21), 210(100), 192 (20), 148 (20), 133(16), 105 (93), 91 (84), 77 (29), HRMS m/z calcd for $C_{19}H_{21}NO_2Na$ 318.1475, found 318.1479.

***N*-Benzyl-2,2-dimethyl-4-oxo-4-phenylbutyramide (9)**: MS (EI) m/z (rel intensity in %) 295 (M^+, 2), 277(2), 262 (2), 175 (5), 161(4), 147 (28), 106 (100), 91 (30), 77 (21).

***N*-Benzyl-3,3-dimethyl-4-oxo-4-phenylbutyramide (10)**: MS (EI) m/z (rel intensity in %) 295 (M^+, 4), 282 (1), 210(7), 190 (11), 174 (1), 148(8), 105 (100), 91 (58), 77 (22).

5-Hydroxy-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (13)

The title compound was obtained from imide (**12**) (559 mg, 3.6 mmol) and isolated by column chromatography on silica gel using gradient cyclohexane to cyclohexane : EtOAc (1:2 v/v) as eluent with yield 83% (697 mg, 3.0 mmol). Recrystallized from $CHCl_3$ mp 198-200 ºC. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.43 (s, 3H), 0.95 (s, 3H), 1.09 (s, 3H), 1.37 (s, 3H), 3.02 (s, 1H, exchangeable with D_2O), 6.90 (s, 1H, exchangeable with D_2O), 7.35 (m, 3H), 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 19.5, 25.1, 25.6, 46.7, 48.2, 91.9, 126.2, 128.3, 128.4, 141.3, 184.0; IR (KBr, cm^{-1}) 3250, 3925, 1660, 1450; MS (ES) $[M+Na]^+ = 256$, $[2M+Na]^+ = 489$, HRMS m/z calcd for $C_{14}H_{19}NO_2Na$ 256.1313, found 265.1315.

3-Methyl-3,5-diphenyl-1,3-dihydropyrrol-2-one (16)

The title compound was obtained from imide (**15**)[18] (681 mg, 3.6 mmol) and isolated by column chromatography on silica gel using $CHCl_3$, as eluent with yield 69 % (619 mg, 2.5 mmol). Recrystallized from $CHCl_3$ mp 153-155 ºC. ^1H NMR ($CDCl_3$, 500 MHz) δ 1,73 (s, 3H), 5.89 (d, *J*=2 Hz, 1H), 7.24 (m, 1H), 7.33 (m, 3H), 7,40 (t, *J*=7.5 Hz 2H), 7.49 (d, *J*=7,5 Hz, 1H), 7.55 (d, *J*=7.5 Hz, 2H), 9.32 (1, 1H, disappeared with D_2O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.5, 54.4, 111.6, 124.8, 126.5, 127.1, 128.6, 128.9, 129.0, 129.8, 139.6, 140.6, 184.3; MS (ES) $[M+Na]^+ = 272$, $[2M+Na]^+ = 521$; HRMS m/z calcd for $C_{17}H_{15}NONa$ 272.1051, found 272.1048.

PROCEDURE FOR ACID TREATMENT OF PHENYLLITHIUM ADDITION PRODUCTS

5-Hydroxy-3,3-dimethyl-5,6-diphenylpiperidin-2-one (11)

Hydroxylactame **8** (50 mg, 0.17 mmol) was dissolved in 10 mL of CH_2Cl_2 and 1 mL of TFA was added. After 48 h solution was extracted twice with aqueous $KHCO_3$ solution and twice with brine. Organic phase was dried over anhydrous $MgSO_4$ and chromatrographed on silica eluting with EtOAc: cyclohexane (1:1 v/v) giving **11** with yield 90% (45 mg, 0.15 mmol). Recrystallized from EtOAc mp, 174-176ºC; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 (s, 3H), 1.54 (s, 3H), 2.27 (q_{AB}, *J*=14.5Hz, 2H), 5.03 (s,

1H), 6.03 (bs, 1H, exchangeable with D_2O), 6.93 (d, *J*=7.0Hz, 2H), 7.18 (t, *J*=7.0Hz, 2H), 7.20-7.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.1, 30.2, 37.6, 48.6, 66.5, 125.2, 127.6, 128.0, 128.4, 128.7, 128.9, 136.0, 144.1, 179.0; MS (ES) $[M+H]^+$ = 296, $[2M+H]^+$ = 591; HRMS m/z calcd for $C_{19}H_{21}NO_2Na$ 318.1475, found 318.1470.

GENERAL PROCEDURE FOR OXIDATIVE SPONTINIFICATION

The mixture of 2,2,3,3-tetramethylsuccinonitrile or succinonitrile (7.5 mmol), 3 mL 6N NaOH, 5 mL of EtOH and 3 mL of 24% aqueous H_2O_2 was gently refluxed for 3 hours. Reaction mixture was acidified to pH 2 with 1N HCl and extracted with toluene (5 × 15 mL). Combined organic phases were dried over anhydrous $MgSO_4$, the solvent evaporated under reduced pressure and the solid residue crystallized from EtOAc.

3,3,4,4-tetramethylsuccimide (12). mp 188-190 °C (lit.,[19] mp 188-189 °C). Yield 84%. Spectral data were in accordance with the literature.[19]

Succinic acid. mp 183-185 °C (lit.,[20] mp 189-190 °C). Yield 72%. Spectral data were in accordance with the literature.[20]

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