Zinc Mediated Barbier Type Allylation of Cyclic Imides and Subsequent Coupling Reactions with Carbon Nucleophiles

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Allylations of *N*-benzyl and *N*-methyl cyclic imides were accomplished successfully under mild Barbier type conditions using zinc metal, allyl bromide and catalytic amount of $PbBr_2$. Subsequent coupling reactions with some carbon nucleophiles afforded 1,2- and 1,4-addition products in moderate to high yields.

Key Words : Allylation, Cyclic imide, Barbier, *N*-Acyliminium ion, Carbon nucleophiles

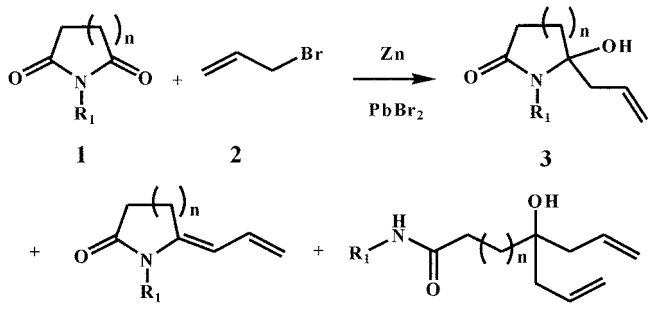
Introduction

Recently, Barbier type allylation reactions are extensively studied with aldehyde,[1] ketone,[2] imine,[3] acetal[4] and nitrile,[5] but Barbier type allylation with cyclic imides have not been well studied in the literature[6] to our knowledge. Reported allylation reactions of cyclic imides have been restricted within 5-membered ring and organomagnesium, organolithium[6] or organozinc reagent[7] under anhydrous condition with moderate yields. As part of our interest in the chemistry of cyclic *N*-acyliminium ions, we reported that the zinc mediated Barbier type propargylation of cyclic imides proceeded well.[8] Recently, we found that zinc mediated Barbier type allylation of cyclic imides also proceeded very well to give allylated hydroxy lactames without the formation of allylidene compounds or recovery of starting materials. Furthermore, we found that *in situ* generated *N*-acyliminium ions can be reacted with carbon nucleophiles such as allyl tri-*n*-butyltin, trimethylsilyl cyanide and 2,4-pentanedione to introduce second substituents to the lactams (Scheme 1).

Results and Discussion

First, we wish to summarize the results of Barbier type allylation of cyclic imides. To a mixture of cyclic imides, metals, catalyst and solvent was added allyl bromide. Among the metals such as In, Zn, Mg, Sn, Fe, Cu, Pb, Al and catalysts such as $ZnCl_2$, $MgBr_2$, $TiCl_4$, $SnCl_4$, $PbBr_2$, $GaCl_3$ and $BF_3{\cdot}Et_2O$, combination of Zn and $PbBr_2$ gave best

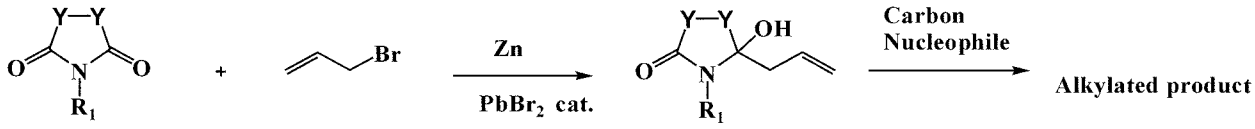
Table 1. Zinc mediated Barbier type allylation of cyclic imides



$R_1 = CH_3$, benzyl, n = 0, 1, 2

entry	cyclic imides	R_1	solvent	isolated yield		
				3	**4**	**5**
1	n = 1	Bn	THF:Et_2O = 1:1, rt	78	10	3
2	n = 1	Bn	THF, rt	50	–	28
3	n = 1	Bn	THF, 0-5 °C	88	–	–
4	n = 1	CH_3	THF, rt	60	30	–
5	n = 1	CH_3	1,4-dioxane, rt	65	21	–
6	n = 1	CH_3	THF, –5-0 °C	86	–	–
7	n = 2	Bn	THF, rt	–	–	85
8	n = 2	Bn	THF, –5-0 °C	–	–	98
9	n = 3	Bn	THF, rt	–	–	90
10	phthalimide	Bn	THF, 0-5 °C	95	–	–

All reactions were carried out 2.5-5 mmol scale, 2 equiv. of zinc granule and 2-2.5 equiv. of allyl bromide were used.



$R_1 = CH_3, CH_2Ph$

Y-Y : CH_2-CH_2, C_6H_4

Scheme 1

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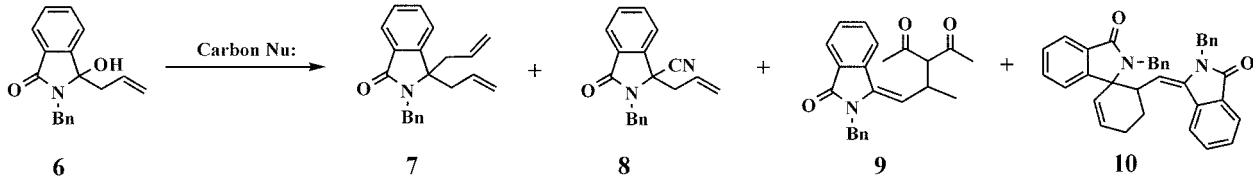
results. Actually, the use of $PbBr_2$ as catalyst[9] was essential to ensure the completion of the reaction to provided allylated α-hydroxy lactams in high yields without the recovery of cyclic imides. It was reported that the use of chemically activated zinc increased the yields of Reformatsky reaction[10a,b] and pulsed sono-electrochemically produced zinc powder greatly increased yield of Barbier type allylation.[10c] However, zinc granule purchased from Aldrich without further activation gave good results in our experiments. The hydroxy-lactams **3**[11] were exclusively obtained when the reactions were carried out at 0-5 °C. Higher temperature, strong Lewis acid catalyst or quenching with 0.5 M HCl led to increased formation of allylidenes **4**. Also, hydroxy-lactam **3** can be easily converted to **4** in the presence of acid catalyst. Attempts to purify the product by silica gel chromatography led to slight decomposition to allylidene **4**. In the case of larger cyclic imides such as *N*-benzylglutarimide and *N*-benzyladipimide, major products are ring-opened di-allylated compounds **5**.[12] These results are summarized in Table 1.

All reactions were carried out 2.5-5 mmol scale, 2 equiv. of zinc granule and 2-2.5 equiv. of allyl bromide were used.

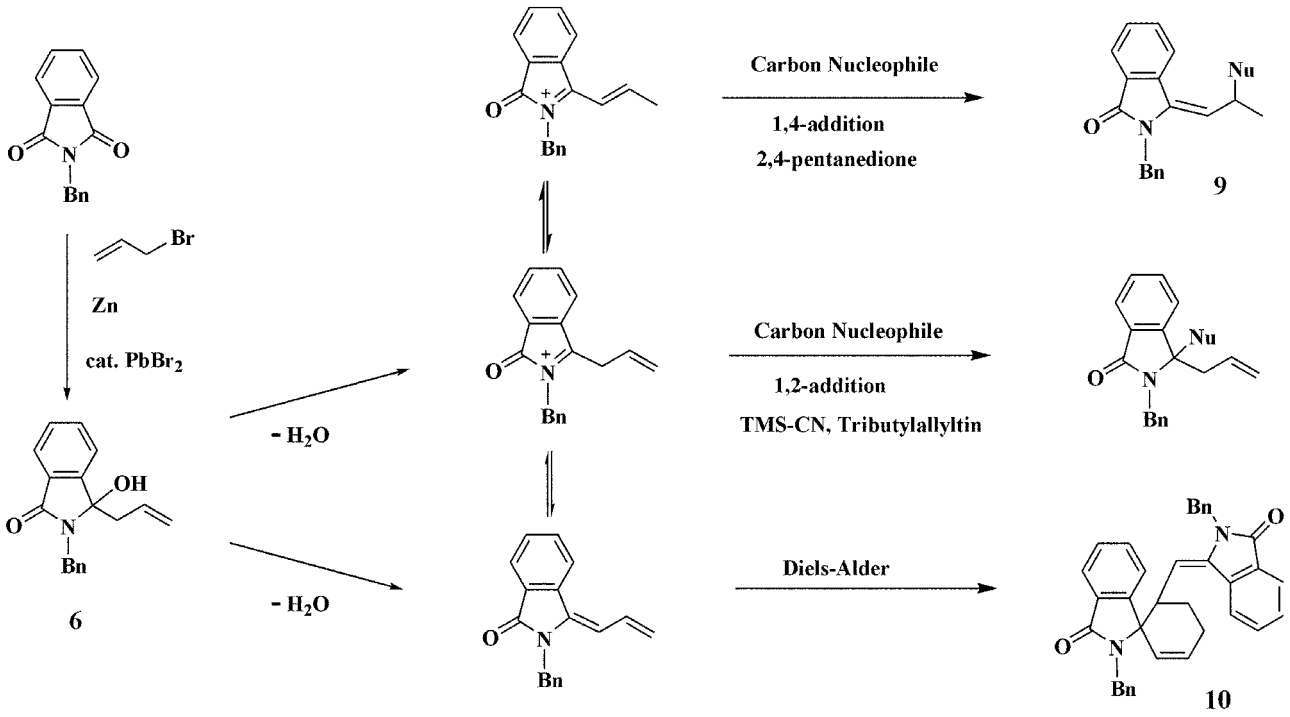
Second, we wish to report the results of alkylation of Barbier type allylation product with carbon nucleophiles. Reactions between *N*-acyliminium ions and nucleophiles have been frequently utilized to introduce substituents at the α-carbon of an amine.[12] The addition of Grignard reagents and organolithium species to cyclic imide, followed by reaction with Et_3SiH,[14] allyltributyltin[6c] has been studied. However, to the best of our knowledge, efforts regarding the creation of a α,α-diallylation and cyanation through the addition of a second carbon nucleophile are not studied well. So, we have examined *in situ* alkylation reactions of 3-allyl-2-benzyl-3-hydroxy-2,3-dihydroisoindol-1-one (**6**) with

Table 2. Coupling reactions of allylated *N*-benzylphthalimide



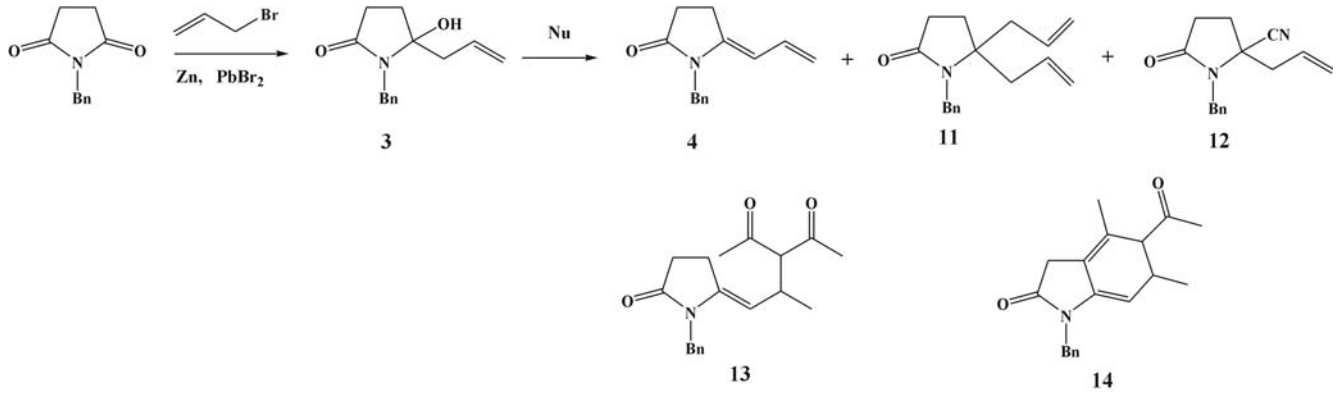
6 **7** **8** **9** **10**

Entry	carbon nucleophile	reaction condition	isolated yield
11	allyltributyltin	BF_3OEt_2, MC, –78 °C → 0 °C, 1 d	**7** (98%)
12	trimethylsilyl cyanide	BF_3OEt_2, MC, 0 °C → rt, 1.5 h	**8** (45%)
13a	2,4-pentanedione	BF_3OEt_2, MC, –78 °C → 0 °C, 1 d	**9** (18%)
13b	2,4-pentanedione	120 °C, neat condition, 2 h	**9** (33%) + **10** (65%)
13c	–	120 °C, AcOH, THF, 2 h	**10** (93%)



Scheme 2

Table 3. Coupling reaction with allylated *N*-benzylsuccinimide



Entry	Carbon Nucleophile	reaction condition	isolated yield
14	allyltributyltin	$BF_3{\cdot}OEt_2$, MC, –78 °C → 0 °C, 1 d	**4** (51 %) + **11** (23%)
15	trimethylsilyl cyanide	$BF_3{\cdot}OEt_2$, MC, 0 °C → rt, 1.5 h	**12** (55%)
16a	2,4-pentanedione	55 °C, THF, 3 d.	**13** (58%)
16b	2,4-pentanedione	120 °C, neat condition, 1 d.	**13** (29%) + **14** (32%)
16c	2,4-pentanedione	55 °C, AcOH, THF, 1 d.	**13** (32%) + **14** (64%)

All reaction was preceded by addition for concerned, *in situ* generated γ-hydroxy lactam **3**.

carbon nucleophiles such as allyltributyltin,[6d] trimethylsilyl cyanide[13] and 2,4-pentanedione to give 1,2- and 1,4-addition products (Table 2).

The BF_3OEt_2 promoted the addition of allyltributyltin, trimethylsilyl cyanide to **6** afforded 5,5-disubstituted isoindolones. On the other hand, other results were observed from the addition of β-diketone. Under similar condition, slow addition reaction proceeded *via* the formation of immediate *N*-acyliminium ion, rearranged to more stable conjugated *N*-acyliminium ion to give 1,4-addition product **9** in 18% yield (entry 13a). Reaction of **6** in 2,4-pentanedione at 120 °C gave **9**[15] and dimeric product **10** (entry 13b). Upon heating of **6** to 120 °C in acetic acid, dimeric compound **10**[16] was obtained in good yield. The structure of **10** is prove to be Diels-Alder product (entry 13c, 1 : 1 mixture of *endo*- and *exo*- products). (Scheme 2).

In another set of experiments, *in situ* alkylation reactions of allylated *N*-benzylsuccinimide **3** were tested with nucleophiles such as allyltributyltin, trimethylsilyl cyanide and 2,4-pentanedione to give 1,2- and 1,4-addition products (Table 3). Enamide formation **4** arise, if the *N*-acyliminium ion is not trapped fast enough by a nucleophile.

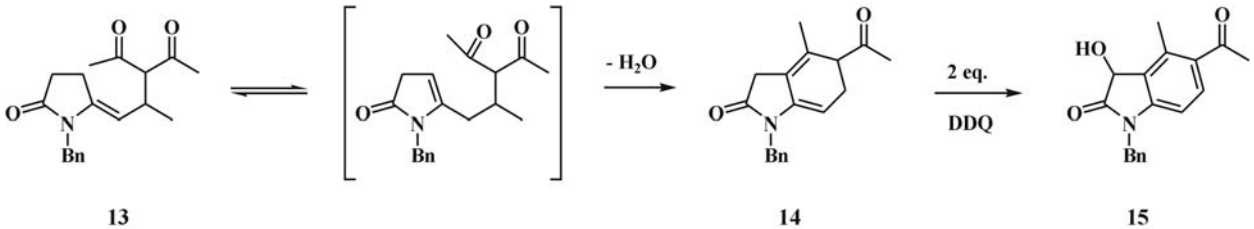
All reaction was preceded by addition for concerned, *in situ* generated γ-hydroxy lactam **3**.

On the other hands, another results were observed in the addition of β-diketone with enol content to *in situ* generated γ-hydroxy lactam **3** at 55 °C giving alkylation product **13**[17] in 58% yield (entry 16a). Upon heating to 120 °C, a mixture of two adducts **13** : **14**[18] was obtained in 61% yield. Also, in the presence of acetic acid a mixture of two adducts **13** : **14** was increased quantitatively in 96 % yield (entry 16c).

To confirm the structure of cyclization product **14**, the reaction mixture was treated with 2 eq of DDQ to give 5-acetyl-1-benzyl-3-hydroxy-4,6-dimethyl-1,3-dihydroindol-2-one **15** with 76% yield[19] (Scheme 3).

Experimental Section

Allylation of cyclic imides. To a mixture of *N*-benzylsuccinimide (5 mmol), zinc granule (10 mmol) and catalytic amount of $PbBr_2$ in THF (10 mL) was added ally bromide (10 mmol) slowly at 0-5 °C, stirred for 5 h until it became sticky greenish gray slurry. The reaction mixture was quenched with aq. NH_4Cl solution (30 mL), then extracted with methylene chloride (2×50 mL). The methylene chloride solution was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give almost pure **3** (88%) which was crystallized out from ether/hexane to



Scheme 3

give as a white solide (entry 3): mp 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1-7.3 (m, 5H), 5.4-5.5 (m, 2H), 4.9-5.0 (m, 2H), 4.6 (d, 1H), 4.3 (d, 1H), 2.4 (m, 2H), 1.9-2.2 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 138.7, 132.4, 128.8, 128.4, 127.5, 119.7, 92.4, 44.4, 42.8, 32.2, 29.5.

To a mixture of *N*-benzylglutarimide (1 mmol), zinc granule (2.5 mmol) and catalytic amount of $PbBr_2$ in THF (10 mL) was added ally bromide (2.5 mmol) slowly at 0-5 °C**,** stirred for 5 h until it became sticky greenish gray slurry. The reaction mixture was quenched with aq. NH_4Cl solution (10 mL), then extracted with methylene chloride (2 × 20 mL). The methylene chloride solution was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give almost pure **5** (98%, entry 8)**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45-1.49 (m, 2H), 1.83 (m, 2H), 2.20-2.25 (m, 6H), 4.4 (d, 2H), 5.08-5.13 (m, 4H), 5.79-5.86 (m, 2H), 7.26-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 37.0, 38.6, 43.9, 44.0, 119.1, 127.8, 128.2, 129.0, 134.0, 138.7, 173.1.

To a mixture of *N*-benzyladipimide (1 mmol), zinc granule (2.5 mmol) in THF (10 mL) was added ally bromide (2.5 mmol) slowly at 0-5 °C, stirred for 5 h until it became sticky greenish gray slurry. The reaction mixture was quenched with aq. NH_4Cl solution (10 mL), then extracted with methylene chloride (2 × 20 mL). The methylene chloride solution was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give almost pure **5**(90%, entry 9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34-1.43 (m, 4H), 1.58-1.62 (q, 2H), 2.16-2.20 (m, 6H), 4.3 (d, 2H), 5.05-5.11 (m, 4H), 5.75-5.84 (m, 2H), 6.45 (s, 1H), 7.22-7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 26.1, 36.4, 38.6, 43.4, 43.6, 73.3, 118.5, 127.3, 127.7, 128.6, 133.8, 138.5, 173.1.

Coupling reactions of allylated *N*-benzylphthalimide. To a solution of **6** (5 mmol) in methylene chloride (25 mL), under an argon atmosphere at −78 °C was added allyl tri-*n*-butyltin followed by BF_3OEt_2 dropwise. The reaction mixture was quenched with 5% $NaHCO_3$ solution (30 mL), then extracted with methylene chloride (2 × 50 mL). The methylene chloride layer was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give almost pure diallylated product **7** (98%, entry 11): mp 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 (m, 4H), 7.2 (m, 5H), 4.9 (m, 2H), 4.6 (d, 2H), 4.5 (m, 4H), 2.5 (2, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 147.8, 138.7, 132.5, 132.0, 131.4, 129.4, 129.1, 128.8, 128.5, 127.8, 122.1, 121.1, 119.5, 69.4, 43.4, 41.9.

To a solution of **6** (2.01 mmol) in methylene chloride(10 mL), under an argon atmosphere at −3 °C was added trimethylsilyl cyanide followed by BF_3OEt_2 dropwise. The reaction mixture was quenched with sat. Na_2CO_3 solution (10 mL), then extracted with methylene chloride (2 × 20 mL). The methylene chloride layer was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give α,α-disubstituted product **8** (45%, entry 12): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8 (d, 1H), 7.5 (m, 3H), 7.3 (d, 2H), 7.2 (m, 3H), 5.0 (m, 1H), 4.9 (d, 2H), 4.7 (m, 2H), 2.8-2.6 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 141.7, 136.5, 133.3, 130.9, 130.7, 129.1, 128.5, 127.8, 124.8, 122.8, 122.7, 117.2, 61.8, 45.1, 41.7.

Coupling reaction with allylated *N*-benzylsuccinimide. To a solution of **3** in methylene chloride, under argon atmosphere at −78 °C was added allyltributyltin followed by BF_3OEt_2 dropwise. The reaction mixture was quenched with 5%. $NaHCO_3$ solution (30 mL), then extracted with methylene chloride (2 × 50 mL). The methylene chloride solution was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give 5-allylidene-1-benzylpyrrolidin-2-one **4** in 51% yield and the formation of addition product **11** in 23% yield (entry 14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.13 (m, 5H), 5.4 (m, 2H), 4.95 (dd, 4H), 4.3 (d, 1H), 4.4 (s, 2H), 2.3 (m, 2H), 2.2 (m, 2H), 2.0 (m, 2H), 1.8 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 139.0, 132.7, 128.8, 128.6, 127.6, 119.7, 72.2, 66.4, 43.9, 43.6, 30.2, 27.8.

To a solution of **3** (1 mmol) in methylene chloride (10 mL), under argon atmosphere at −78 °C was added trimethylsilyl cyanide (3 mmol) followed by BF_3OEt_2 dropwise. The reaction mixture was quenched with 5%. $NaHCO_3$ solution (30 mL), then extracted with methylene chloride (2 × 50 mL). The methylene chloride solution was washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated to give α,α-disubstituted product **12** in 55% yield (entry 15): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 5H), 5.5 (m, 1H), 5.2 (dd, 2H), 4.8 (d, 1H), 4.4 (d, 1H), 2.6 (m, 3H), 2.4 (m, 1H), 2.26 (m, 1H), 2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 136.8, 129.1, 128.6, 128.4, 122.6, 119.5, 72.2, 61.6, 45.3, 42.8, 30.4, 29.1.

Conclusions

We have demonstrated a efficient and convenient method of Barbier type allylations of cyclic imides was accomplished under mild condition in excellent yields and applied to the further *in situ* reactions with various carbon nucleophiles to afford in highly fnctionalized 5,5-disubstituted isoindolones, spirocyclization compound. We also found that β-diketone as carbon nucleophile can be used as precursors for a π-nucleophilic attack onto allylated hydroxy lactams, giving 1,2-addition products. So, allylated hydroxy lactams have proven a useful *N*-acyliminium ion precursor in coupling reaction. We are currently studying reactions of allylated hydroxy lactams with some other carbon nucleophiles in order to investigate their utilization in the total synthesis of natural compounds.

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11. mp 88 °C; NMR data of 5-allyl-1-benzyl-5-hydroxypyrrolidin-2-one **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1-7.3 (m, 5H), 5.4-5.5 (m, 2H), 4.9-5.0 (m, 2H), 4.6 (d, 1H), 4.3 (d, 1H), 2.4 (m, 2H), 1.9-2.2 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 138.7, 132.4, 128.8, 128.4, 127.5, 119.7, 92.4, 44.4, 42.8, 32.2, 29.5.
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15. NMR data of 3-[2-(2-benzyl-3-oxo-2,3-dihydroisoindol-1-ylidene)-1-methylethyl]pentane-2,4-dione (**9**) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.9 (dd, 2H), 7.5 (td, 2H), 7.3-7.1 (m, 5H), 5.0 (dd, 2H), 4.9 (d, 1H), 3.9 (m, 1H), 3.5 (d, 1H), 2.1 (s, 3H), 1.7 (s, 3H), 0.9 (d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 166.8, 137.2, 135.4, 135.2, 132.8, 130.9, 129.7, 129.1, 127.8, 127.2, 124.2, 114.2, 75.9, 43.3, 32.7, 30.6, 29.7, 19.9.
16. NMR data of Diels-Alder product **10**: (a) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (d, 1H), 7.7 (d, 1H), 7.6 (m, 2H), 7.3-7.1 (m, 6H), 6.8 (m, 3H), 6.7 (d, 2H), 6.6 (t, 2H), 6.4 (t, 1H), 6.0 (m, 1H), 5.0 (d, 1H), 4.9 (d, 1H), 4.5 (dd, 2H), 4.3 (d, 1H), 4.0 (d, 1H), 3.2 (m, 1H), 2.3 (m, 2H), 2.1 (m, 1H), 1.7 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.4, 150.4, 139.2, 136.6, 135.9, 135.0, 133.1, 132.6, 132.3, 131.0, 130.9, 129.3, 129.1, 128.9, 128.8, 128.6, 127.8, 127.7, 127.6, 126.9, 124.3, 124.2, 122.9, 121.6, 111.3, 67.8, 60.8, 46.1, 43.1, 41.8, 26.2, 25.4, 21.5, 14.6. (b) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.1 (d, 1H), 7.9 (d, 1H), 7.8 (m, 2H), 7.6 (t, 1H), 7.5-7.4 (m, 11H), 7.2 (m, 2H), 6.5 (m, 1H), 5.4 (d, 1H), 5.2 (dd, 2H), 5.1 (d, 1H), 4.7 (d, 1H), 4.6 (d, 1H), 3.9 (m, 1H), 2.6 (m, 2H), 2.0 (m, 3H).
17. NMR data of 3-[1-methyl-2-(5-oxo-1-phenylpyrrolodin-2-ylidene)-ethyl]pentane-2,4-dione (**13**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.1-7.2 (m, 5H), 5.0 (d, 1H), 4.2 (d, 1H), 4.1 (d, 1H), 3.3 (d, 1H), 2.9 (m, 1H), 2.6 (m, 2H), 2.5 (m, 2H), 2.0 (s, 3H), 1.6 (s, 3H), 0.8 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 202.8, 175.7, 140.1, 135.9, 128.6, 128.4, 127.3, 126.9, 103.5, 75.2, 53.5, 43.4, 33.1, 31.1, 29.1, 28.6, 21.1, 19.7
18. NMR data of 5-acetyl-1-benzyl-4,6-dimethyl-1,3,5,6-tetrahydro-indol-2-one (**14**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2-7.1 (m, 5H), 4.7 (d, 1H), 4.5 (d, 1H), 4.4 (d, 1H), 3.1 (s, 2H), 2.7 (s, 1H), 2.6 (m, 1H), 2.0 (s, 3H), 1.6 (s, 3H), 0.8 (d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 173.5, 138.2, 136.2, 128.9, 127.6, 127.5, 125.4, 122.8, 97.6, 62.0, 44.0, 33.2, 31.5, 28.6, 22.4, 18.9. Mass; M^+ (295), M-15 (280), M-43 (252).
19. NMR data of 5-acetyl-1-benzyl-3-hydroxy-4,6-dimethyl-1,3-di-hydroindol-2-one (**15**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3 (m, 5H), 6.4 (s, 1H), 5.1 (s, 1H), 4.9 (d, 1H), 4.8 (d, 1H), 2.4 (s, 3H), 2.3 (s, 3H), 2.1 (s, 3H), 1.5 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 172.4, 143.4, 138.3, 136.1, 135.1, 131.9, 129.1, 128.0, 127.2, 121.7, 109.4, 51.2, 44.1, 32.6, 20.1, 15.8.