Single-Step Symmetrical Double Alkylation of β,γ-Unsaturated δ-Lactams via Magnesium 'Ate' Complexes

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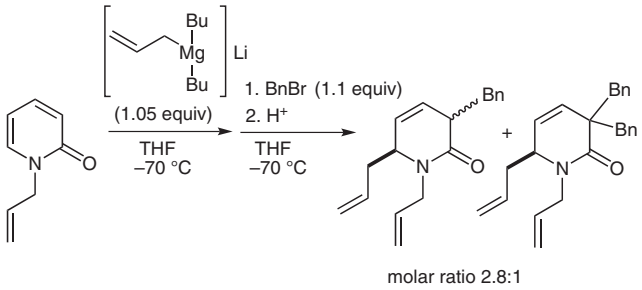
Abstract: An easy approach to symmetrically 3,3-dialkylated derivatives of 3,6-dihydro-1*H*-pyridin-2-one in a one-pot and a single-step procedure via magnesium 'ate' complex is described. [Bu_3Mg]Li used as the base showed great basic potential as one equivalent of it allowed double proton abstraction from 3,6-dihydro-1*H*-pyridin-2-one. Deprotonation at noncryogenic conditions yielded stable magnesiates which on treatment with more than two equivalents of alkyl halides provided 3,3-dialkylated products in good yield. In some cases minor 3,5-dialkylated lactams were formed due to allylic conjugation.

Key words: lactams, magnesium 'ate' complex, alkylation, piperidines

Magnesium 'ate' complexes have been known since Wittig and co-workers described formation of lithium triphenylmagnesiate ([Ph_3Mg]Li) from its homometallic components (PhLi and Ph_2Mg) in 1951.[1] However their application in the synthesis has been explored intensively only in the past decade. The main interest has been focused on halogen–magnesium exchange reactions[2] and only little attention has been devoted to magnesiates as alkylating agents.[1,3] Recently, much work has been carried out to explore [R_3Mg]Li as bases.[4] Deprotonative property of magnesium 'ate' complexes has been used mainly in proton abstraction from the aromatic compounds like activated benzenes, pyridines,[5] oxazoles,[6] furans,[7] and thiophenes.[8] There are only few examples of the use of the magnesium 'ate' complexes as deprotonating agents able to eliminate H from sp^3 carbon site.[9]

Among our recent efforts on the synthesis of functionalized δ-lactams[10] and δ-thiolactams,[11] we have previously reported on nucleophilic properties of lithium allyldibutylmagnesiate {[$AllylBu_2Mg$]Li}. This magnesium 'ate' complex, prepared by mixing of allylmagnesium chloride and *n*-butyllithum in 1:2 molar ratio at 0 °C, allowed a regioselective introduction of an allyl substituent onto a piperidine ring.[11c,12,13] Addition of lithium allyldibutylmagnesiate to *N*-methylpyridin-2-one at 0 °C yielded mainly 6-allyl-1-methyl-3,6-dihydro-1*H*-pyridin-2-one,[12] while added to *N*-allylpyridin-2-ones at –70 °C led exclusively to 1,6-diallyl-3,6-dihydro-1*H*-pyridin-2-ones.[13] The synthesis of the latter allowed us to obtain racemic 3,6,9,9a-tetrahydro-quinolizin-4-ones by ring-closing metathesis (RCM).[13]

In the preliminary studies on 3-alkylation of 1,6-diallyl-3,6-dihydropyridin-2-ones in the reaction of the adduct, formed from lithium allyldibutylmagnesiate and *N*-allylpyridin-2-one, with 1.1 equivalents of BnBr at –70 °C, the formation of minor 3,3-dibenzylated β,γ-unsaturated δ-lactam apart from 3-monobenzylated derivatives was observed (Scheme 1).[13] This observation prompted us to investigate the possibility of 3,3-dialkylation of β,γ-unsaturated δ-lactams using magnesiates. The goal seemed to be interesting in the aspect of further disclosing applications of magnesiates as reagents and because the quaternization adjacent to the carbonyl group is still a challenging problem in synthetic organic chemistry.[14] Moreover, 3,3-dialkyl substituted δ-lactams exhibited interesting biological activity.[15]



Scheme 1

The hitherto applied double alkylation of lactams at C-α relative to carbonyl, also in the introduction of the same substituents,[16] was frequently realized by successive treatment of lactam with organolithium bases like: *s*-BuLi, LDA, or LiHMDS followed by addition of alkyl electrophiles after each equivalent of base used.[17] Symmetrical dialkylation in one-step protocol using two equivalents of lithium bases at once at the beginning of the reaction was only sparingly applied.[18] Moreover, double alkylation of β,γ-unsaturated δ-lactams at C-α was not reported, while monoalkylation was achieved by trapping of lithium[19] or cuprate[20] dienolates with electrophiles.

In this Letter we describe the preliminary results on a new one-step symmetrical double alkylation of β,γ-unsaturated δ-lactams via magnesium 'ate' complexes, generated by proton abstraction from β,γ-unsaturated δ-lactams us-

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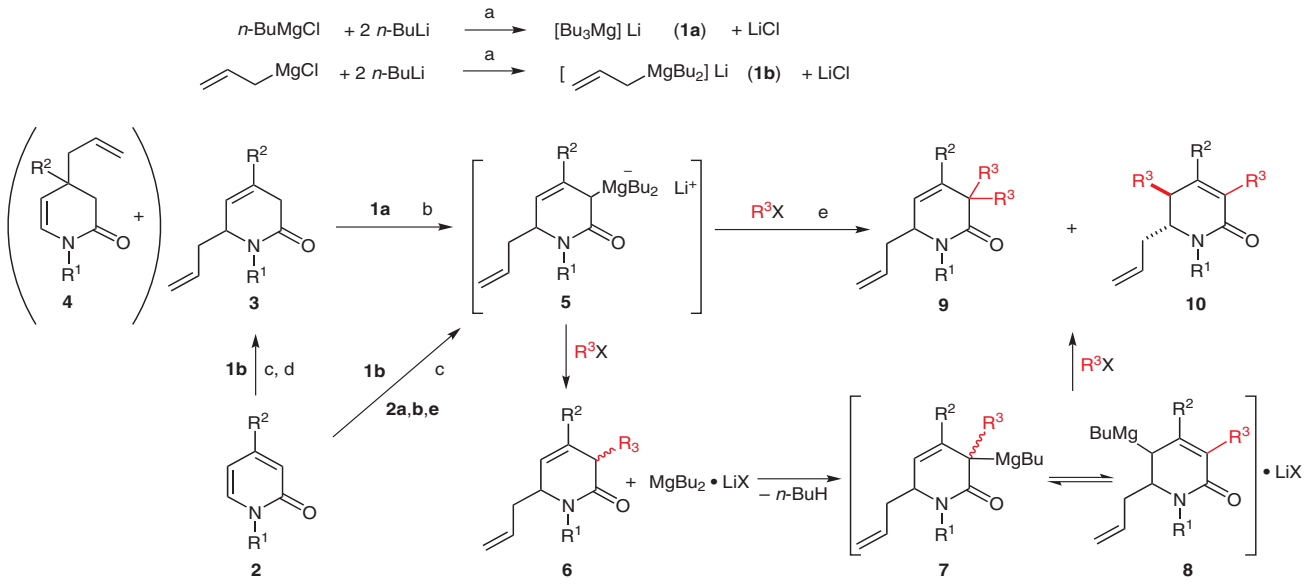

Scheme 2 *Reagents and conditions*: (a) THF, 0 °C 5 min; (b) **1a** (1.05 equiv), 0 °C, 0.5 h; (c) **1b** (1.05 equiv), –72 °C, 15 min; (d) aq NH_4Cl; (e) R^3X (> 2.0 equiv), 0 °C, 0.5–1 h.

ing [Bu_3Mg]Li or by addition of [AllylBu$_2$Mg]Li to pyridin-2-ones.

At the first stage *N*-Me-, *N*-allyl-, *N*-Bn- and *N*-Ph-substituted 6-allyl-3,6-dihydro-1*H*-pyridin-2-ones **3a–d** were obtained as model compounds and were subsequently submitted to the reaction with 1.05 equivalents of [Bu_3Mg]Li (Scheme 2, **1a**) prepared simply by mixing of *n*-BuMgCl and *n*-BuLi in 1:2 molar ratio. Deprotonations were performed at 0 °C for 0.5 hours in a THF solution.

Subsequently, addition of more than two equivalents of primary alkyl halides (benzyl bromide, allyl bromide, and *n*-propyl iodide) provided double 3,3-dialkylation (product **9**) within 30–60 minutes in good yields (Scheme 2, Table 1).[21] In the case of allyl bromide and propyl iodide, formation of small quantity of 3,5-dialkylated products **10** was also observed.

Substrates **3a–d** were obtained according to the procedure described earlier,[12,13] involving the addition of **1b** to the corresponding N-substituted pyridin-2-ones **2**, however,

Table 1 Reaction Conditions, Yields, and Ratio of **9/10** Obtained in a Single-Step Dialkylation of **3** Using [Bu_3Mg]Li (**1a**)

Entry	**3**[a]	R^1	R^3X (equiv)	**9**, **10**	Ratio of **9/10**[b]	Yield of **9** and **10** (%)[d]
1	**3a**	Me	BnBr (2.2)	**9a, 10a**	>99:1	94
2	**3a**	Me	AllBr (3.0)	**9b, 10b**	83:17	76
3	**3a**	Me	*n*-PrI (2.3)	**9c, 10c**	96:4	81
4	**3b**	Allyl	BnBr (2.2)	**9d, 10d**	>99:1	72
5	**3b**	Allyl	AllBr (3.0)	**9e, 10e**	89:11	60
6	**3b**	Allyl	*n*-PrI (2.3)	**9f, 10f**	95:5	70
7	**3c**	Bn	BnBr (2.3)	**9g, 10g**	>99:1	98
8	**3c**	Bn	AllBr (3.0)	**9h, 10h**	90:10	89
9	**3c**	Bn	*n*-PrI (2.3)	**9i, 10i**	97:3	87
10	**3d**	Ph	BnBr (2.3)	**9j, 10j**	99:1	98
11	**3d**	Ph	AllBr (3.0)	**9k, 10k**	92:8	94
12	**3d**	Ph	*n*-PrI (2.3)	**9l, 10l**	75:25[c]	72

[a] R^2 = H.
[b] Ratio estimated by ^{1}H NMR spectroscopy unless stated otherwise.
[c] Ratio estimated by ^{13}C NMR spectroscopy.
[d] Total isolated yield.

in the present study low temperatures (–72 °C) were applied (Scheme 2, Table 2). Since the low temperature applied in the above reactions provided **3a**, **3b**, and **3e** regioselectively, the synthesis of **9a–f** and **9m–s** (Scheme 2, Table 3) was possible in a one-pot procedure starting from **2a**, **2b**, and **2e**. Thus, magnesium 'ate' complexes of **2a**, **2b**, and **2e** generated as a result of addition of 1.05 equivalent of lithium allyldibutylmagnesiate (**1b**) at –72 °C and trapped with alkyl halides (>2.0 equiv), after stirring at 0 °C provided double alkylated products in good yields (Scheme 2, Table 3). At this stage, in order to check the generality of the proposed strategy, the broader spectrum of alkyl halides was used in the reaction with magnesium 'ate' complex obtained from **2a** (Table 3, entries 1–6).

The reaction course of the worked-out synthesis of **9** is presented in Scheme 2. Dibutylmagnesiated lactam **5**, formed from **3** and **1a** or **2** and **1b**, being stable near 0 °C, led to monoalkylated product **6** in the reaction with the first equivalent of RX. Dibutyl magnesium ($MgBu_2$) formed in this reaction together with LiX,[22] also present in the reaction mixture, is basic enough[23] to abstract proton from monoalkylated lactam **6** producing butylmagnesiated lactam **7** and **8** due to allylic conjugation. Since **7** is well stabilized by carbonyl conjugation (not seen) product **9** is obtained in great majority as a result of the reaction with second equivalent of alkyl halide.

With respect to the 3,3- or 3,5-dialkylation regioselectivity, BnBr and decyl iodide reacted the most regioselectively and provided mainly 3,3-dialkylated product. However, it should be noted that 4-methyl substituent in **2e** diminished 3,3-dibenzylation, yielding 3,3- (**9p**) and 3,5-dibenzylated (**10p**) products in 91:9 molar ratio (Table 3, entry 10).

As far as the basicity of $[Bu_3Mg]Li$ is concerned the above investigations led to the conclusion that trialkylmagnesium 'ate' complex has great basic potential because it enables twice repeated proton abstraction. The preferred monoalkylation at a low temperature (ca. –70 °C, Scheme 1) and dialkylation possible near 0 °C indicated different nucleophilic power of **5** and **7**, **8** after the first and the second deprotonation steps.

Structures of **3**, **9**, and **10** were determined on the basis of 1D NMR (^1H, ^{13}C, ^{13}C-DEPT), 2D NMR (^1H, ^1H COSY, ^{13}C, ^1H COSY) spectroscopy.[24] Additionally, conformational analysis of **10p** using the coupling constants and molecular modelling as well as ^1H,^1H NOESY spectrum was applied to establish 5,6-*trans* configuration in **10**. Although a distinct cross-peak found in the NOESY spec-

Table 2 Preparation of **3** According to the Procedure Presented in Scheme 2

Entry	**2**	R^1	R^2	**3**, **4**	Ratio of **3/4**[a]	Yield of **3** and **4** (%)[b]
1	**2a**	Me	H	**3a, 4a**	100:0	81
2	**2b**	Allyl	H	**3b, 4b**	99:1	79
3	**2c**	Bn	H	**3c, 4c**	95:5	83
4	**2d**	Ph	H	**3d, 4d**	69:31	93
5	**2e**	Allyl	Me	**3e, 4e**	100:0	91

[a] Ratio estimated by ^1H NMR spectroscopy.
[b] Total isolated yield.

Table 3 Reaction Conditions, Yields, and Ratio of **9/10** Obtained in a One-Pot Sequentional Addition of **1b** to **2** Followed by Dialkylation

Entry	**2**	R^1	R^2	R^3X (equiv)	**9**, **10**	Ratio of **9/10**[a]	Yield of **9** and **10** (%)[c]
1	**2a**	Me	H	BnBr (2.2)	**9a, 10a**	>99:1	92
2	**2a**	Me	H	AllylBr (2.9)	**9b, 10b**	85:15	76
3	**2a**	Me	H	*n*-PrI (2.3)	**9c, 10c**	97:3[b]	64
4	**2a**	Me	H	MeI (3.0)	**9m, 10m**	95:5	69
5	**2a**	Me	H	*i*-Bu (2.2)	**9n, 10n**	83:17[b]	72
6	**2a**	Me	H	*n*-DecylI (2.2)	**9o, 10o**	>99:1	72
7	**2b**	Allyl	H	BnBr (2.2)	**9d, 10d**	>99:1	84
8	**2b**	Allyl	H	AllylBr (3.0)	**9e, 10e**	86:14	71
9	**2b**	Allyl	H	*n*-PrI (2.2)	**9f, 10f**	97:3	73
10	**2e**	Allyl	Me	BnBr (3.0)	**9p, 10p**	91:9	88
11	**2e**	Allyl	Me	AllylBr (3.0)	**9r, 10r**	80:20	62
12	**2e**	Allyl	Me	*n*-PrI (2.5)	**9s, 10s**	95:5	66

[a] Ratio estimated by ^1H NMR spectroscopy unless stated otherwise.
[b] Ratio estimated by ^{13}C NMR spectroscopy.
[c] Total isolated yield (%).

trum between H-5 and H-6 of **10p** indicated a short distance between them in the molecule, the routine ^{1}H, ^{1}H COSY spectra gave no visible cross-peak indicating the absence or a small value of the vicinal coupling constants. Indeed, $^3J_{H\text{-}5,H\text{-}6}$ coupling constant refined from Lorentzian to Gaussian resolution enhancement spectra was established as ca. 1 Hz. According to the Haasnoot equation[25] this value corresponds to H-5/H-6 dihedral angle of 79° and is in good agreement with the angle of 83° present in 5,6-*trans*-disubstituted structure of **10p** optimized by PM3 calculation.[26]

In conclusion, we have demonstrated new and efficient single-step, double-alkylation protocol of N-substituted 6-allyl-3,6-dihydro-2*H*-pyridin-2-ones performed in non-cryogenic conditions using lithium tributylmagnesiate (**1a**) as a base followed by treatment with primary alkyl halides (> 2.0 equiv). Double proton abstraction achieved by using of one equivalent of tributyl magnesium 'ate' complex revealed its great basic potential. It should be emphasized that due to the combination of highly convertible amide and alkenyl groups present in lactam, as well as a broad range of electrophiles potentially used for the dialkylation, the method proposed stand as valuable approach to functionalized piperidines. Investigation of the possibilities and limitations of the 3,3-dialkylation of lactams via trialkylmagnesium 'ate' complexes as well as the possible synthesis of spirofunctionalized δ-lactams in the reaction with 1,n-dihalogenoalkanes and by 3,3-dialkenylation–RCM is currently under way.

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(21) **Typical Procedure for the Dialkylation of 3 Using [Bu_3Mg]Li (1a)**
To a cooled (0 °C) and stirred solution of BuMgCl (2.1 mmol, 1.05 mL, 2.0 M in THF) in dry THF (2 mL) in a Schlenk flask, *n*-BuLi (4.2 mmol, 1.68 mL, 2.5 M in hexane) was added via syringe over 1 min under argon. A yellow suspension formed was stirred for 5 min and was next transferred via syringe to a cooled (0 °C) solution of 6-allyl-1-methyl-3,6-dihydro-1*H*-pyridin-2-ones (**3a**, 0.3 g, 2.0 mmol) in THF (10 mL). The resulting yellow solution was stirred for 30 min at 0 °C, and then benzyl bromide (0.75 g, 4.4 mmol) was added and stirred for 30 min. After addition of aq sat. NH_4Cl (5 mL), the aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layers were dried over $MgSO_4$. Filtration, concentration in vacuo, and purification by flash column chromatography (silica gel, *n*-hexane–EtOAc = 8:2, next 7:3) yielded **9a**.

(22) Due to a well documented enhancement effect of LiCl on the reactivity of Grignard reagents it is possible that the presence of LiX (X = Cl, I) in the reaction environment influenced basicity of $MgBu_2$, see: Rauhut, C. B.; Vu, A. V.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2008**, *10*, 1187; and references cited therein, see also ref. 23a.

(23) (a) Kerr, W. J.; Watson, A. J. B.; Hayes, D. *Chem. Commun.* **2007**, 5049; and references cited therein. (b) Richey, H. G. Jr.; King, B. A. *J. Am. Chem. Soc.* **1982**, *104*, 4672.

(24) **Selected Spectroscopic Data**
6-Allyl-3,3-dibenzyl-1-methyl-3,6-dihydro-1*H*-pyridin-2-one (9a)
Colorless solid (0.62 g, 94%), mp 61–63 °C (from *n*-hexane). IR (KBr pellet): ν = 3028 (w), 2912 (w), 1628 (s), 1496 (w), 1456 (w), 1398 (w), 1348 (w), 1230 (w), 916 (w), 756 (m), 744 (m), 702 (m), 696 (m) cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.03 (1 H, dt, *J* = 14.0, 8.3 Hz, 6-CHH), 1.86 (1 H, dm, *J* = 14.0 Hz, 6-CHH), 2.65 (2 H, d, *J* = 12.6 Hz, 2 × 3-CHH), 2.69 (3 H, s, NCH_3), 3.14–3.20 (1 H, m, CH-6), 3.44 (1 H, d, *J* = 12.6 Hz, 3-CHH), 3.47 (1 H, d, *J* = 12.6 Hz, 3-CHH), 4.70–4.80 (2 H, m, $=CH_2$), 4.92–5.05 (1 H, m, =CH), 5.42 (1 H, dd, *J* = 10.3, 3.2 Hz, =CH-5), 5.54 (1 H, dd, *J* = 10.3, 1.6 Hz, =CH-4), 7.08–7.27 (10 H, m, 2 × C_6H_5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 32.46 (NCH_3), 38.20 (6-CH_2), 45.93, 46.58 (2 × 3-CH_2), 50.54 (C-3), 59.03 (CH-6), 117.86 ($=CH_2$), 125.33 (=CH-5), 128.80 (=CH-4), 126.20, 126.35, 127.54, 127.79, 130.30, 130.66, 137.61, 137.82 (2 × C_6H_5), 132.61 (=CH), 170.80 (C-2). GC-MS (EI, 70eV): *m/z* = 331 (<1) [M^+], 290 (100), 198 (28), 122 (37), 91 (63). Anal. Calcd for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.25; H, 7.69; N, 4.13.

(25) Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, A. *Tetrahedron* **1980**, *36*, 2783.

(26) PM3 calculations were performed using the HyperChem program (7.52 release).