Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6809–6812

Convenient approach to tetrahydro-quinolizin-4-ones by sequential addition of lithium allyldibutylmagnesate to *N*-allylpyridin-2-ones and ring-closing metathesis reactions

Jacek G. Sośnicki*

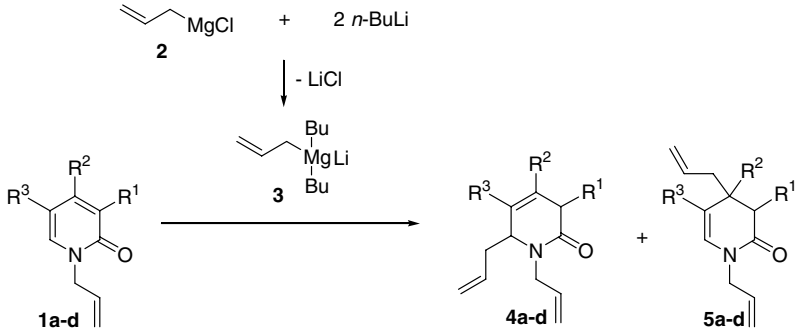
Technical University of Szczecin, Institute of Chemistry and Environmental Protection, Al. Piastów 42, PL-71065 Szczecin, Poland

Received 2 June 2006; revised 4 July 2006; accepted 14 July 2006
Available online 8 August 2006

Abstract—A new strategy based on allylation of *N*-allylpyridin-2-ones with the lithium allyldibutylmagnesate reagent followed by ring-closing metathesis in a sequential fashion to access the quinolizidine skeleton with olefinic bonds in both rings is reported.

Organic compounds containing the quinolizidine skeleton are widespread in naturally occurring alkaloids and in biologically active compounds.[1] Ring-closing metathesis (RCM) has emerged as a powerful method for the synthesis of quinolizidines[2,3] and related azaheterocycles.[4,5] Common synthetic approaches toward quinolizidines and related systems, based on RCM methodology, consist of the introduction of one of two adjacent allyl groups by the addition reaction of allyl nucleophiles to *N*-acyliminium ions of azaheterocycles.[3,5] Among recent efforts on the synthesis of functionalized piperidines, we have previously reported a new and regioselective method for the introduction of an allyl substituent onto a piperidine ring using the novel magnesium 'ate' complex, lithium allyldibutylmagnesate.[6] One of the few examples described was the synthesis of 6-allyl-1-methyl-3,6-dihydro-1*H*-pyridin-2-one obtained from *N*-methylpyridin-2-one.

In the present letter, we demonstrate that this methodology together with RCM reactions can be used in order to provide a new access to quinolizidin-4-ones, containing olefin bonds in both rings. Such compounds, which due to the presence of double bonds can be considered as valuable precursors for further functionalization, are rare and have been hitherto



Scheme 1.

Keywords: Quinolizidines; Lithium magnesates; Magnesium 'ate' complex; Allylation; Pyridin-2-ones; RCM.
* Tel.: +48 91 4494798; fax: +48 91 4494639; e-mail: sosnicki@ps.pl

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.07.072

obtained from acyclic alkenes via double ring-closing metathesis.[2d–f]

The lithium allyldibutylmagnesate reagent (**3**, Scheme 1) prepared simply by mixing of 1.1 equiv of allylMgCl (in THF) and 2.2 equiv of *n*-BuLi was sufficiently nucleophilic to react at low temperature (−70 °C) with *N*-allyl substituted pyridin-2-one **1a** as well as with *N*-allylpyridin-2-ones possessing methyl substituents attached to the ring (**1b–d**, Scheme 1). Under these conditions, the reactions proceeded smoothly with complete conversion after 20 min to give the 6-allylation products **4** in excellent yields and regioselectivities (Scheme 1, Table 1). Only in the case of 5-methyl substituted pyridin-2-one **1d** was slightly lower regioselectivity observed (**4**:**5** = 91:9). An attempt to allylate 3-methylpyridin-2-one (**1b**) allowed verification of the stereoselectivity at C-3. In this reaction, low stereoselectivity was observed yielding trans and cis isomers of **4b** in the ratio of 60:40, however, these compounds could easily be obtained in diastereoisomerically pure state by flash column chromatography.

For the sake of comparison, **1a** was exposed to allylMgCl (**2**) under the same reaction conditions and, as expected from previous observations,[6] the results confirmed a low reactivity relative to that of allyl-Bu_2MgLi (**3**) (Table 1, entry 1).

Encouraged by the above results, we were prompted to check if it would be possible to obtain 3-functionalized *δ*-lactams in one pot, starting with the allylation of **1** and by subsequent quenching of the reaction on treatment with electrophiles. This one-pot protocol was tested on derivative **1a** using BnBr as the electrophile, and resulted in the formation of the 3-benzyl derivatives **6** in moderate yields and with significant stereoselectivity at C-3 with preference for trans isomer **6a**. Surprisingly, double benzylation at C-3 was also observed (product **7**, Scheme 2).[7]

Finally, the synthesis of quinolizidin-4-one derivatives was performed. Thus, 1,6-diallyl β,γ-unsaturated *δ*-lactams **4**, **6**, and **7** were submitted to RCM reactions. The cyclization, conducted in CH_2Cl_2 at room temperature, employing 8 mol % of Grubbs' catalyst **10**, was complete in 2 h and products **9** were isolated in high yields (Scheme 3).[8]

All compounds are new and their structures were confirmed by spectroscopic methods.

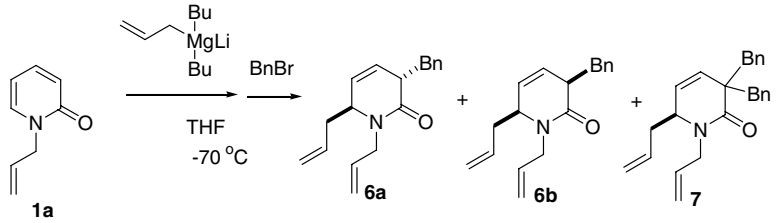
The configurations of products **4b** (trans), **4b** (cis), **6a**, and **6b** were determined on the basis of 1D NOE or 2D ^1H, ^1H NOESY spectra.

In conclusion, we have demonstrated that the addition of lithium allyldibutylmagnesate reagent **3** to *N*-allylpyridin-2-ones followed by RCM provides easy access to racemic 3,6,9,9a-tetrahydro-quinolizin-4-ones, possessing C–C double bonds in both rings. The protocol described could be extended to the synthesis of substituted quinolizidines, via synthesis of the corresponding β,γ-unsaturated *δ*-lactams, in which the substituent originates from the starting *N*-allylpyridin-2-one (3-,4-,5-substituted) or could be introduced in one pot after allylation (3-substituted). Due to the high degree of functionalization, the quinolizidin-4-ones obtained can be employed as versatile building blocks in natural product synthesis. Further work is ongoing to determine the full value of this methodology.

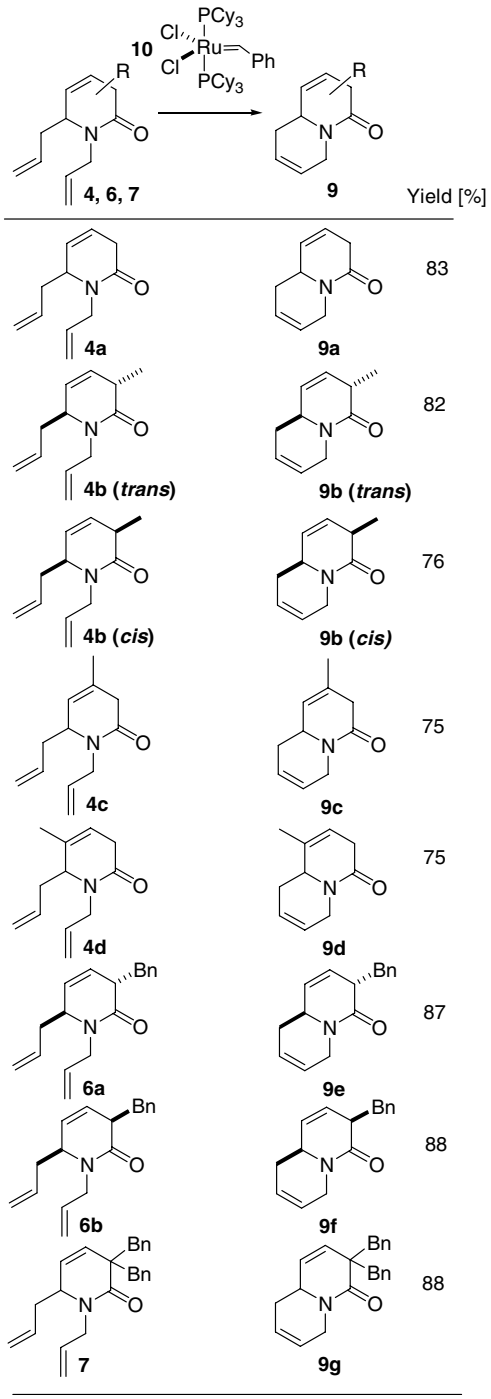
Table 1. Reaction conditions, ratios and yields of **4**:**5**

Entry	Reagent	Pyridin-2-one	R^1	R^2	R^3	Temp (°C)	**4**:**5** ratio[a]	**4**:**5** ratio[b]	Conversion (%)[a]	Yield (%)[b]
1	**2**	**1a**	H	H	H	−70	76:24	75:25	54	27
2	**3**	**1a**	H	H	H	−70	99:1	98:2	>99	83
3	**3**	**1b**	CH_3	H	H	−70	98:2 (60:40):(50:50)[c]	97:3 (60:40):(0:0)[c]	>99	90
4	**3**	**1c**	H	CH_3	H	−65	100:0	100:0	>99	90
5	**3**	**1d**	H	H	CH_3	−70	91:9	90:10	>99	89

[a] Estimated by ^1H NMR of the crude reaction mixture.
[b] Isolated yield.
[c] Trans:cis ratio is given in the parenthesis.



Scheme 2.



Scheme 3. Reagents and conditions: 8 mol % **10**, CH_2Cl_2, rt, 2 h.

Acknowledgments

This work was supported in part by a grant from the National Committee for Scientific Research (KBN, Grant No. 3 T09A 106 28). The support by the Department of Technology and Chemical Engineering, Technical University of Szczecin, is gratefully acknowledged.

References and notes

1. For a leading review of quinolizidine alkaloids, see: Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625–649.
2. (a) Katoh, M.; Mizutani, H.; Honda, T. *Tetrahedron Lett.* **2005**, *46*, 5161–5163; (b) Kinderman, S. S.; De Gelder, R.; Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Am. Chem. Soc.* **2004**, *126*, 4100–4101; (c) Diedrichs, N.; Westermann, B. *Synlett* **1999**, 1127–1129; (d) Ma, S.; Ni, B.; Liang, Z. *J. Org. Chem.* **2004**, *69*, 6305–6309; (e) Krelaus, R.; Westermann, B. *Tetrahedron Lett.* **2004**, *45*, 5987–5990; (f) Ma, S.; Ni, B. *Org. Lett.* **2002**, *4*, 639–641.
3. (a) Wijdeven, M. A.; Botman, P. N. M.; Wijtmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. *Org. Lett.* **2005**, *7*, 4005–4007; (b) Chen, B.-F.; Tasi, M.-R.; Yang, C.-Y.; Chang, J.-K.; Chang, N.-C. *Tetrahedron* **2004**, *60*, 10223–10231; (c) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695–1701; (d) Overkleeft, H. S.; Bruggeman, P.; Pandit, U. K. *Tetrahedron Lett.* **1998**, *39*, 3869–3872.
4. (a) Gracias, V.; Gasiecki, A. F.; Djuric, S. W. *Org. Lett.* **2005**, *7*, 3183–3186; (b) Mori, M.; Wakamatsu, H.; Tonogaki, K.; Fujita, R.; Kitamura, T.; Sato, Y. *J. Org. Chem.* **2005**, *70*, 1066–1069; (c) Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716–3721; (d) Duggan, H. M. E.; Hitchcock, P. B.; Young, D. W. *Org. Biomol. Chem.* **2005**, *3*, 2287–2295; (e) Amat, M.; Perez, M.; Minaglia, A. T.; Casamitjana, N.; Bosch, J. *Org. Lett.* **2005**, *7*, 3653–3656; (f) Desroy, N.; Robert-Peillard, F.; Toueg, J.; Hénaut, C.; Duboc, R.; Rager, M.-N.; Savignac, M.; Genet, J.-P. *Synthesis* **2004**, *16*, 2665–2672; (g) Manzoni, L.; Colombo, M.; Scolastico, C. *Tetrahedron Lett.* **2004**, *45*, 2623–2625; (h) Davoli, P.; Spaggiari, A.; Ciamaroni, E.; Forni, A.; Torre, G.; Prati, F. *Heterocycles* **2004**, *63*, 2495–2514; (i) Arjona, O.; Csáky, A. G.; Leon, V.; Medel, R.; Plumet, J. *Tetrahedron Lett.* **2004**, *45*, 565–567; (j) Lee, H. K.; Chun, J. S.; Pak, C. S. *J. Org. Chem.* **2003**, *68*, 2471–2474; (k) Park, S. H.; Kang, J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621–2624; (l) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179–1180.
5. (a) Langlois, N.; Le Nguyen, B. K.; Retaillau, P.; Tarnus, C.; Salomon, E. *Tetrahedron: Asymmetry* **2006**, *17*, 53–60; (b) Burgess, K. L.; Lejkiewicz, N. J.; Sanyal, A.; Yan, W.; Snyder, J. K. *Org. Lett.* **2005**, *7*, 31–34; (c) Colombo, L.; Di Giacomo, M.; Vinci, V.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 4501–4513; (d) Hannessian, S.; Sailes, H.; Munro, A.; Therrien, E. *J. Org. Chem.* **2003**, *68*, 7219–7233; (e) El-Nezhawy, O. H.; El-Diwani, H. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 4137; (f) Neipp, C. E.; Martin, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779–1782; (g) Schuch, M. C.; Pilli, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 753–764; (h) Lennartz, M.; Steckhan, E. *Synlett* **2000**, 319–322; (i) Maldaner, A. O.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 7843–7846; (j) Grossmith, C. E.; Senia, F.; Wagner, J. *Synlett* **1999**, 1660–1662; (k) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1998**, *63*, 7893–7907; (l) Beal, L. M.; Moeller, K. *Tetrahedron Lett.* **1998**, *39*, 4639–4642.
6. Sośnicki, J. G. *Tetrahedron Lett.* **2005**, *46*, 4295–4298.
7. The procedure for the preparation of **6a**, **6b**, and **7** was as follows: To a cooled (0 °C) and stirred solution of 9.8 mmol of allylMgCl (4.9 ml, 2.0 M in THF) in dry THF (10 ml) in a Schlenk flask, 19.6 mmol of *n*-BuLi (7.8 ml, 2.5 M in hexane) was added via a syringe over 3 min under argon. A white suspension formed, which was stirred for 5 min and cooled to −70 °C. The suspension containing lithium allyldibutylmagnesate was next transferred via a syringe

to a cooled (−70 °C) solution of *N*-allylpyridin-2-one (**1a**, 1.2 g, 8.9 mmol) in THF (40 ml). The resulting brown-orange solution was stirred for 20 min at −70 °C and then BnBr (1.67 g, 10.0 mmol) in THF (5 ml) was added over 5 min and stirred for 20 min. After quenching with aqueous saturated NH_4Cl (15 ml), the aqueous layer was extracted with ethyl acetate (2 × 100 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/ethyl acetate = 8:2 then 7:3) yielded **6a**, **6b**, and **7** in 44%, 9%, and 19% yields, respectively. Selected spectroscopic data: **6a** (*trans*-1,6-diallyl-3-benzyl-3,6-dihydro-1*H*-pyridin-2-one). Colorless oil. IR (film): $\nu = 3028$, 2924, 1640, 1456, 1344, 1262, 996, 920, 742, 700 cm^{-1}. MS (EI, 70 eV): $m/z = 267$ (M^+, 1), 226 (100), 176 (7), 134 (11), 120 (9), 115 (9), 91 (100), 65 (16), 41 (16); ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 2.29$ (1H, dm, $J = 14.5$ Hz, 6-C*H*H), 2.38 (1H, dt, $J = 14.5$, 7.3 Hz, 6-CH*H*), 2.94 (1H, dd, $J = 13.4$, 8.7 Hz, 3-C*H*H), 3.18–3.24 (1H, m, CH-3), 3.33 (1H, dd, $J = 13.4$, 4.2 Hz, 3-CH*H*), 3.52 (1H, dd, $J = 15.5$, 7.0 Hz, NC*H*H), 3.87 (1H, ddd, $J = 6.3$, 5.9, 3.0 Hz, CH-6), 4.69 (1H, ddt, $J = 15.5$, 4.4, 1.7 Hz, NCH*H*), 5.02–5.14 (4H, m, 2 × =CH_2), 5.59–5.74 (4H, m, 2 × =CH, =CH-4, =CH-5), 7.17–7.29 (5H, m, C_6H_5); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 37.47$ (6-CH_2), 38.08 (3-CH_2), 42.03 (CH-3), 46.41 (NCH_2), 56.73 (CH-6), 117.09, 119.23 (2 × =CH_2), 125.18, 126.34 (=CH-4, =CH-5), 126.24, 128.18, 129.61, 138.89 (C_6H_5), 132.03, 132.94 (2 × =CH), 170.22 (C-2); Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.71; H, 8.09; N, 5.45.

8. General procedure for the preparation of lactams **9**: To a solution of 1,6-diallyl lactam **4a**–**d**, **6**, or **7** (1.0 mmol) in dry CH_2Cl_2 (40 ml), ruthenium catalyst **10** (57.6 mg, 0.07 mmol) was added and the reaction was stirred using a stream of argon slowly bubbled through the solution at rt for 2 h. After evaporation of the solvent at reduced pressure, the residue was dissolved in CH_3OH (5 ml) and silica gel (1 g) and activated carbon (0.25 g) was added and the mixture was kept at rt for 24 h. After evaporation of the solvent, the residue was submitted for column chromatography on silica gel. Selected spectroscopic data: **9c** (2-methyl-3,6,9,9a-tetrahydro-quinolizin-4-one). Colorless oil. IR (film): $\nu = 3036$, 2892, 2840, 1640, 1448, 1408, 1356, 1298, 1248, 816 cm^{-1}. MS (EI, 70 eV): $m/z = 163$ (M^+, 100), 162 (79), 148 (67), 134 (21), 120 (22), 110 (25), 94 (18), 81 (39), 80 (89), 54 (49), 53 (34), 41 (22), 39 (36); ^1H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.73$ (3H, s, CH_3), 2.01–2.13 (1H, m, C*H*H-9), 2.25 (1H, dm, $J =$ ca. 17.1 Hz, CH*H*-9), 2.83–2.99 (2H, m, CH_2-3), 3.49 (1H, d, $J = 18.8$ Hz, C*H*H-6), 4.02 (1H, br dm, $J =$ ca. 6.4 Hz, CH-9a), 4.87 (1H, d, $J = 18.8$ Hz, CH*H*-6), 5.42 (1H, br s, =CH-1), 5.68–5.75 (1H, m, =CH), 5.77–5.83 (1H, m, =CH); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 21.84$ (CH_3), 33.71 (CH_2-9), 36.43 (CH_2-3), 41.87 (CH_2-6), 54.11 (CH-9a), 119.32 (=CH-1), 124.20, 124.23 (2 × =CH), 129.09 (C-2), 166.80 (C-4); HRMS (EI) for $C_{10}H_{13}NO$; calcd 163.09971; found 163.09947.