Tetrahedron Letters 50 (2009) 1696–1698

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Indium-mediated double Barbier reaction of γ-cyanoesters derived from Baylis–Hillman adduct

Sung Hwan Kim, Hyun Seung Lee, Ko Hoon Kim, Jae Nyoung Kim *

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea

ARTICLE INFO

Article history:
Received 18 December 2008
Revised 15 January 2009
Accepted 19 January 2009
Available online 5 February 2009

Keywords:
Indium
Barbier reaction
Lactam
Baylis–Hillman adducts

ABSTRACT

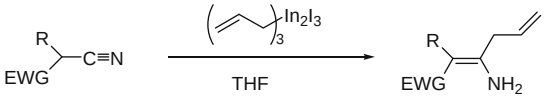
We developed an efficient synthetic method of diallylated δ-valerolactam and γ-butyrolactam derivatives via an indium-mediated successive double Barbier type allylations starting from the Baylis–Hillman adducts.

Allylindium reagents have been used extensively for the introduction of allyl group in a Barbier type manner.[1–3] Although allylindium reagents can be added to many reactive functional groups including aldehyde, ketone, and activated imine with acyl or tosyl group,[1,2] the reaction with nitrile has not been reported except for the recent Yamamoto's paper.[3] According to the results, introduction of allylindium can be carried out with only nitrile compounds having both an α-hydrogen atom and an α-EWG group (Scheme 1).[3]

Recently Baylis–Hillman adducts have been used for the synthesis of various cyclic compounds.[4,5] Among them, many of the interesting cyclic compounds were synthesized from the suitably modified Baylis–Hillman adducts with active methylene compounds like ethyl cyanoacetate, dimethyl malonate, and ethyl acetoacetate.[5] Based on the Yamamoto's results,[3] we reasoned that we could prepare the allylated pyridine derivative (**III**) by the double bond isomerization of compound **4a**, which could be prepared from the Baylis–Hillman acetate **1a** as in Scheme 2.[5a] However, we obtained diallyl compound **5a** as the major product presumably via the second introduction of allyl group to the reactive cyclic *N*-acylimine intermediate (**II**), the tautomer of **4a**. This type of consecutive double allylation reaction has not been reported to the best of our knowledge.

Encouraged by the results, we examined the generality of this successive In-mediated Barbier type allylation with γ-cyanoesters **3a–d**. The starting materials **3** were prepared by the reaction of Baylis–Hillman acetates (**1a–c**)/bromide (**1d**) and active methylene compounds **2a–c** in the presence of K_2CO_3.[5] With these compounds, we examined the Barbier reaction with in situ generated allylindium reagent from allyl bromide and indium powder in THF. Mono-allylated compounds **4a–d** were isolated in low yields (12–16%). Instead diallylated δ-valerolactam derivatives **5a–d** were obtained as the major products (52–61%).[6,7] The results are summarized in Table 1.

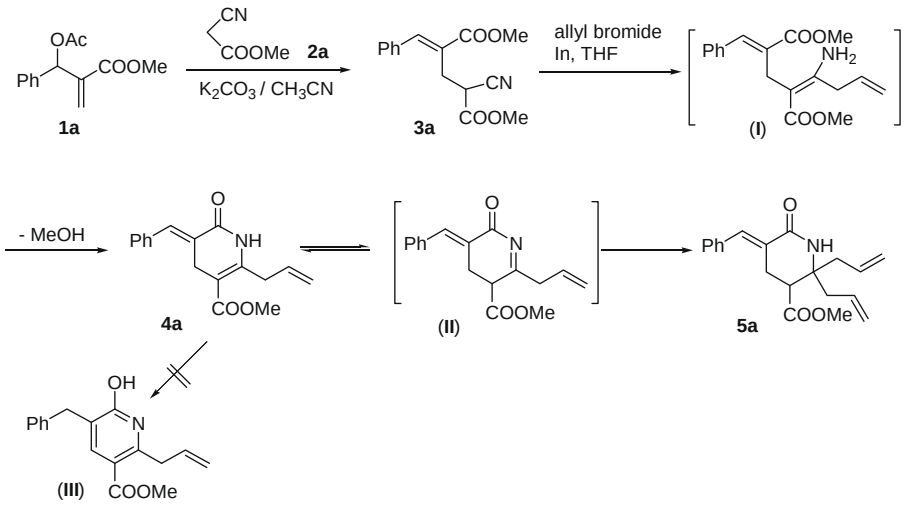
Diallylated compound **5** must be formed by double Barbier reaction via the cyclic *N*-acylimine intermediate (**II**), a tautomer of minor product **4**. As reported, *N*-acylimine is more reactive than nitrile toward allylindium species,[1,2] thus the second allylation occurs to a larger extent to give **5** as the major product. Trials for the synthesis of mono-allylated compound as the major product failed. As next entries, we examined the synthesis of diallylated γ-butyrolactam derivatives via the double-Barbier reaction with **6a** and **6b** (Scheme 3).[6] The starting materials were synthesized from Baylis–Hillman acetates **1c** and **1e** with KCN in good yields.[5d] The following In-mediated allylation reaction provided diallylated compounds **7a** and **7b** in reasonable yields. In these cases we did not observe the formation of appreciable amounts of mono-allylated compounds. The reaction of **6a** with crotyl bromide under the same conditions was very sluggish, unfortunately. Dicrotyl γ-butyrolactam **7c** was obtained in low yield (10%) after 30 h and we recov-



Scheme 1.

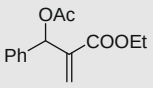
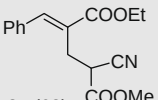
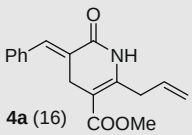
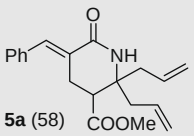
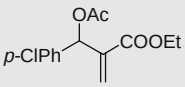
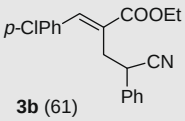
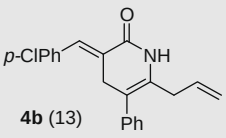
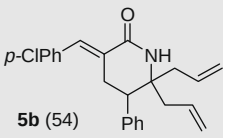
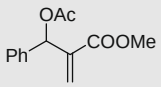
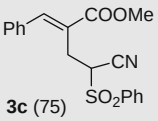
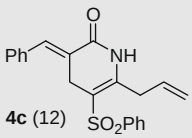
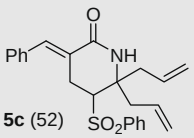
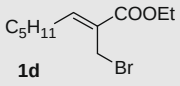
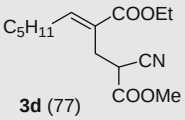
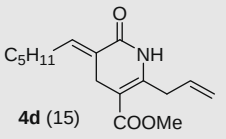
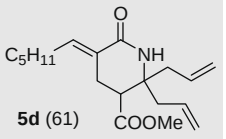
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.
E-mail address: kimjn@chonnam.ac.kr (J.N. Kim).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.01.149



Scheme 2.

Table 1
Synthesis of diallylated lactam **5a**–**d**

Entry	Substrate	Conditions	Compound **3** (%)	Products[a] (%)	
1	 **1a**	$NCCH_2COOMe$ (**2a**), K_2CO_3 (1.5 equiv), CH_3CN, rt, 2 h	 **3a** (68)	 **4a** (16)	 **5a** (58)
2	 **1b**	$NCCH_2Ph$ (**2b**), K_2CO_3 (1.5 equiv), CH_3CN, rt, 3 h	 **3b** (61)	 **4b** (13)	 **5b** (54)
3	 **1c**	$NCCH_2SO_2Ph$ (**2c**), K_2CO_3 (1.5 equiv), CH_3CN, rt, 2 h	 **3c** (75)	 **4c** (12)	 **5c** (52)
4	 **1d**	**2a**, K_2CO_3 (1.5 equiv), CH_3CN, rt, 2 h	 **3d** (77)	 **4d** (15)	 **5d** (61)

[a] Conditions: compound **3** (1.0 equiv), allyl bromide (4.0 equiv), In (2.0 equiv), THF, reflux, 30 min.

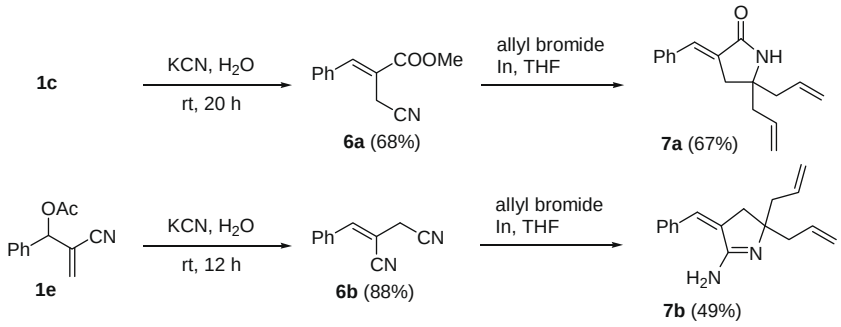
ered **6a** (61%). The compound **8** showed no reaction under the same conditions as expected due to the lack of α-hydrogen atom around nitrile group (Scheme 4).[3]

As one of the synthetic applications of diallylated δ-valerolactam derivatives, we examined the RCM (ring-closing metathesis) reaction of compound **5a** with 2nd generation Grubbs catalyst (3 mol %) in toluene (50 °C, 10 h) and obtained the corresponding spiro-cyclopentene compound **9** in 84% yield (Scheme 5).[8]

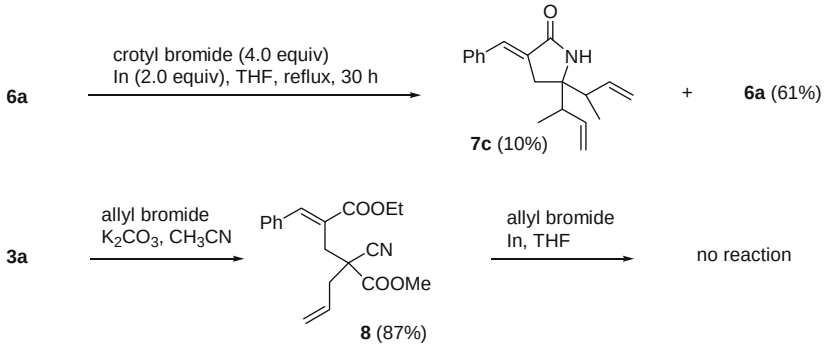
In summary, we disclosed an efficient synthesis of diallylated δ-valerolactam and γ-butyrolactam derivatives via an indium-mediated successive double Barbier type allylations. Further synthetic applications of this interesting double allylation concept are under study.

Acknowledgments

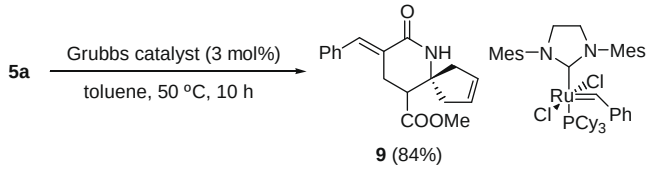
This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2008-313-C00487). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.



Scheme 3.



Scheme 4.



Scheme 5.

References and notes

1. For the general review on indium-mediated reactions, see: (a) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764; (b) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149–11176; (c) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715–737.
2. For the indium-mediated Barbier type allylation of imine, acylimine, sulfonimine and related compounds, see: (a) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464–3471; (b) Schneider, U.; Chen, I.-H.; Kobayashi, S. *Org. Lett.* **2008**, *10*, 737–740; (c) Kumar, H. M. S.; Anjaneyulu, S.; Reddy, E. J.; Yadav, J. S. *Tetrahedron Lett.* **2000**, *41*, 9311–9314; (d) Piao, X.; Jung, J.-K.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 139–142; (e) Ritson, D. J.; Cox, R. J.; Berge, J. *Org. Biomol. Chem.* **2004**, *2*, 1921–1933; (f) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589–8594.
3. (a) Fujiwara, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 4729–4732; (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095–4101.
4. For the general review on Baylis–Hillman chemistry, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (c) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490; (d) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574. and further references cited therein.
5. For the synthesis of starting materials and similar pyridine derivatives from Baylis–Hillman adducts, see: (a) Kim, S. H.; Kim, K. H.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 1948–1951; (b) Zhong, W.; Lin, F.; Chen, R.; Su, W. *Synthesis* **2008**, 2561–2568; (c) Im, Y. J.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1361–1362; (d) Hong, W. P.; Lim, H. N.; Park, H. W.; Lee, K-J. *Bull. Korean Chem. Soc.* **2005**, *26*, 655–657.
6. For the synthesis of similar lactam derivatives and their synthetic applications, see: (a) Pohmakotr, M.; Yotapan, N.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V. *J. Org. Chem.* **2007**, *72*, 5016–5019; (b) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071; (c) Doan, H. D.; Gore, J.; Vatele, J.-M. *Tetrahedron Lett.* **1999**, *40*, 6765–6768; (d) Zhou, C.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2007**, *129*, 5828–5829; (e) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631–3634; (f) Lee, K. Y.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 2007–2011.
7. *Typical procedure for the synthesis of compounds **3a**, **4a** and **5a***: A mixture of compound **1a** (248 mg, 1.0 mmol), methyl cyanoacetate (297 mg, 3.0 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in CH_3CN (3 mL) was stirred at room temperature for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 8:1), we obtained compound **3a** (195 mg, 68%) as colorless oil. A stirred mixture of compound **3a** (144 mg, 0.5 mmol), allyl bromide (242 mg, 2.0 mmol), and indium (114 mg, 1.0 mmol) in THF (1.5 mL) was heated to reflux for 30 min. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 16:2:1), we obtained compound **4a** (23 mg, 16%) and compound **5a** (93 mg, 58%). Other compounds were synthesized similarly and the spectroscopic data of **3a**, **4a**, **5a**, and **7a** are as follows:Compound **3a**: 68%; colorless oil; IR (film) 2958, 2251, 1751, 1703, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, J = 7.2 Hz, 3H), 3.16–3.19 (m, 2H), 3.75 (s, 3H), 4.12 (dd, J = 8.7 and 7.5 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 7.34–7.45 (m, 5H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 27.6, 36.1, 53.4, 61.4, 115.9, 126.8, 128.7, 128.9, 129.0, 134.4, 144.1, 166.0, 168.8.Compound **4a**: 16%; yellow solid, mp 128–129 °C; IR (KBr) 3211, 1709, 1642, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.56–3.59 (m, 2H), 3.75 (s, 3H), 3.79–3.80 (m, 2H), 5.18–5.34 (m, 2H), 5.78–5.91 (m, 1H), 7.30–7.50 (m, 5H), 7.82 (t, J = 2.7 Hz, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.2, 36.0, 51.5, 101.9, 119.4, 125.4, 128.6, 129.0, 130.4, 132.6, 135.0, 138.1, 144.6, 165.3, 167.0; ESIMS m/z 284 (M^++1). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.43; H, 6.35; N, 4.88.Compound **5a**: 58%; pale yellow solid, mp 113–114 °C; IR (KBr) 3178, 1734, 1668, 1614, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.33–2.57 (m, 4H), 2.90–2.97 (m, 1H), 3.09–3.12 (m, 2H), 3.70 (s, 3H), 5.16–5.25 (m, 4H), 5.76–5.92 (m, 2H), 6.20 (s, 1H), 7.29–7.42 (m, 5H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.7, 41.1, 42.6, 45.1, 51.9, 57.5, 120.7 (2C), 126.1, 128.4, 128.5, 129.9, 131.6, 131.6, 135.3, 137.3, 165.8, 172.0; ESIMS m/z 326 (M^++1). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.75; H, 7.34; N, 4.45.Compound **7a**: 67%; pale yellow solid, mp 115–116 °C; IR (KBr) 3201, 1693, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27–2.44 (m, 4H), 2.93 (d, J = 1.8 Hz, 2H), 5.13–5.20 (m, 4H), 5.72–5.86 (m, 2H), 6.23 (s, 1H), 7.31–7.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.3, 44.8, 58.6, 120.1, 128.7, 128.7, 129.6, 130.4, 131.0, 132.0, 135.6, 170.9; ESIMS m/z 254 (M^++1). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.53; H, 7.76; N, 5.72.
8. Compound **9**: 84%; pale yellow solid, mp 132–133 °C; IR (film) 3171, 1733, 1668, 1613, 1394 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44–2.49 (m, 2H), 2.82–3.13 (m, 5H), 3.66 (s, 3H), 5.66–5.71 (m, 2H), 6.30 (s, 1H), 7.30–7.44 (m, 5H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.0, 43.0, 46.5, 47.0, 52.1, 63.3, 126.2, 127.4, 128.4, 128.5, 128.7, 129.9, 135.4, 137.3, 165.3, 172.1; ESIMS m/z 298 (M^++1). For similar spiro-pyridone synthesis, see: Kersten, L.; Taylor, R. H.; Felpin, F.-X. *Tetrahedron Lett.* **2009**, *50*, 506–508.