Efficient Entry to Polysubstituted Pyrrolizidines, Indolizidines and Quinolizidines via a Sequential Reaction Process

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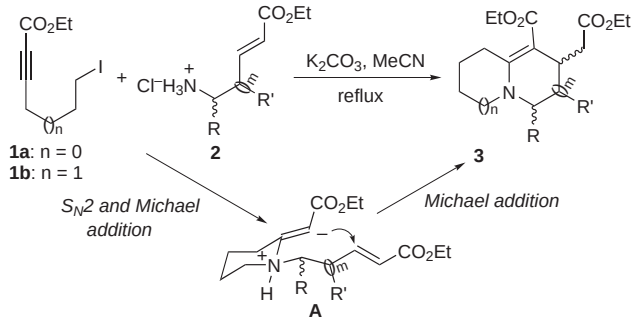
Abstract: A sequential S_N2–Michael addition–Michael addition reaction process between ω-iodo-α,β-alkynoates and δ- or γ-amino α,β-unsaturated esters is developed, which affords polysubstituted pyrrolizidines, indolizidines or quinolizidines in good yields.

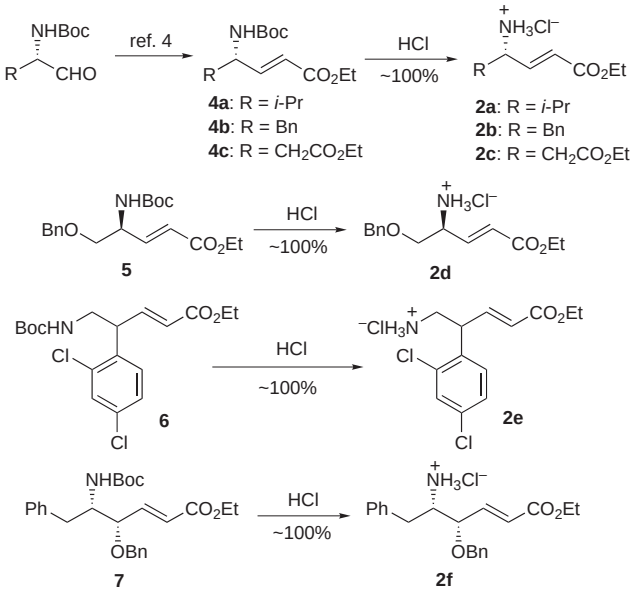
Key words: cascade reactions, pyrrolizidines, indolizidines, quinolizidines

Recently, we have reported several cascade processes using ω-iodo-α,β-alkynoates **1** as bisfunctional building blocks.[1–3] When they reacted with other bisfunctional compounds such as β-amino esters,[1] δ-chloropropylamines,[2] or 2-aryl aziridines,[3] a variety of quinolizidinones, indolizidinones, indolizidines or quinolizidines were obtained. As a continuing effort of this project, we report here a new cascade process employing δ- or γ-amino α,β-unsaturated esters **2** as bisfunctional agents. As depicted in Scheme 1, reaction of **1** and **2** might undergo an S_N2 reaction between the amino group in **2** and the iodide moiety in **1**, and subsequent Michael addition between the resultant secondary amine and the electron-deficient C–C triple bond to provide monocyclic intermediates **A**. The vinylogous anion thus formed would attack another electronic deficient C–C double bond to furnish bicyclic products **3**.



Scheme 1

The requisite δ- or γ-amino α,β-unsaturated esters **2** were generally assembled via a Wittig reaction of the corresponding *N*-Boc amino aldehyde[4] and subsequent treatment with HCl as represented by preparation of **2b–f** (Scheme 2). From diol **8**, a reduction product of Boc-protected L-aspartic acid dimethyl ester, two α,β-unsaturated esters were elaborated (Scheme 3). Swern oxidation of **8** followed by a Wittig reaction provided diene **9** in 45% yield, which was treated with a gaseous hydrogen chloride saturated ethyl acetate solution to afford γ-amino α,β-unsaturated ester **2g**. In a parallel procedure, protection of **8** with DMP produced monoalcohol **10**, which was subjected to Swern oxidation and Wittig olefination to give **11**. Treatment of **11** with TFA and subsequent benzyl ether formation provided **12**, which was exposed on HCl in ethyl acetate to result in δ-amino α,β-unsaturated ester **2h**.



Scheme 2

Elaboration of the other two enantiopure δ-amino α,β-unsaturated esters **2i** and **2j** is demonstrated in Scheme 4. After hydrogenolysis of β-amino ester **13**[1] accompanying with in situ Boc-protection to afford ester **14**, reduction of ester moiety and Swern oxidation were carried out to give an aldehyde, which was reacted with a Wittig reagent to provide olefin **15**. Exposure of **15** on HCl in ethyl acetate furnished **2i**. Similarly, **2j** was obtained from an L-alanine-derived β-amino ester through olefin **16**.

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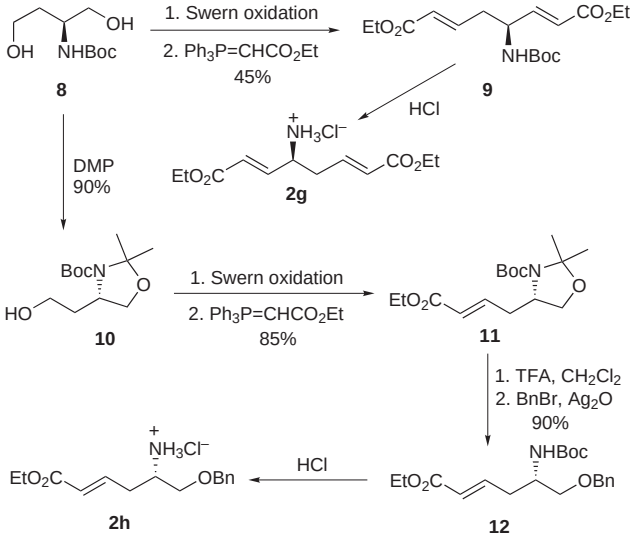
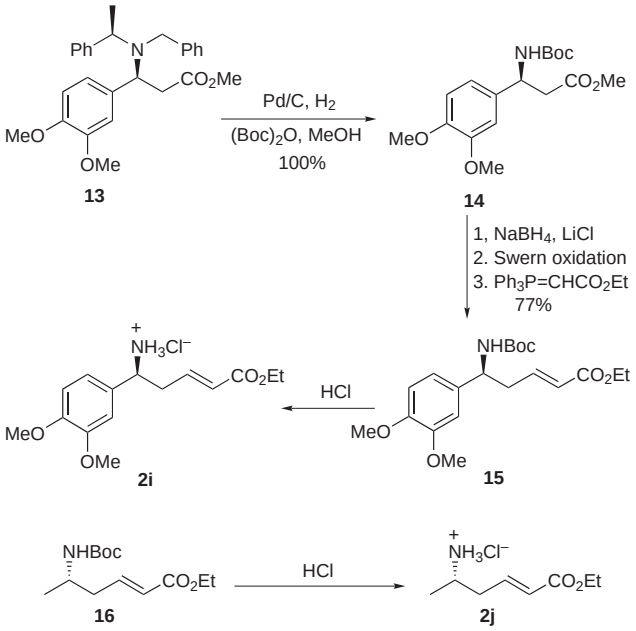


Scheme 3



Scheme 4

With the above δ- or γ-amino α,β-unsaturated esters in hand, we next tried their reaction with ω-iodo-α,β-alkynoates. As summarized in Table 1, heating a mixture of L-valine derived γ-amino α,β-unsaturated ester **2a**, iodide **1b** and K_2CO_3 in MeCN afforded 1,2,3-trisubstituted indolizidine **3a**[5,6] in 80% yield (entry 1). Its stereochemistry was 1,2-*trans* as determined by NOESY, which might result from the strong 1,2-induction during the last Michael addition step. Similarly, indolizidines **3b–d** were obtained from the corresponding L-phenylalanine, L-aspartic acid or L-serine-derived γ-amino α,β-unsaturated ester substrate (entries 2–4). Noteworthy is that we obtained 8-substituted, 5,8-disubstituted and 5,6,8-trisubstituted indolizidines via sequential S_N2–Michael addition–S_N2–S_N2 reaction process.[2] A combination of these two processes would therefore be able to construct more diverse substituted indolizidines.

When methyl 7-iodo-2-hexynoate (**1a**) was used, this process allowed the formation of 1,2,3-trisubstituted pyrrolizidines **3e** and **3f** although the yields were moderate due to incomplete conversion in the last step (entries 5 and 6). In the cases of δ-branched γ-amino α,β-unsaturated esters as substrates, reaction with **1b** produced 1,2,3-trisubstituted quinolizidine **3g** (entry 7), or even 1,2,3,4-tetrasubstituted quinolizidine **3h**[5,7] (entry 8). Their stereochemistry was still 1,2-*trans*, which was the same as that of γ-amino α,β-unsaturated ester derived products due to a similar mechanism. However, when δ-unbranched γ-amino α,β-unsaturated esters were employed, a mixture of two isomers in favor of 1,2-*cis*-isomer formed (entries 9–11). We reasoned that this stereochemistry might be contributed by a chair-like transition state at the intramolecular Michael addition step, in which 1,3-substituents preferred a *cis* relationship in the reactive conformer.

Table 1 Reaction of Iodides **1** and Amines **2**[a]

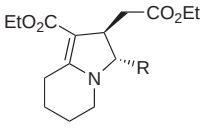
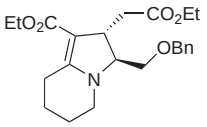
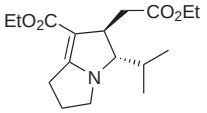
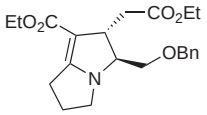
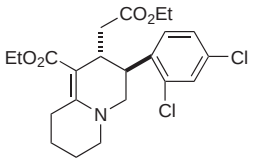
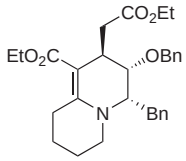
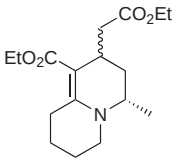
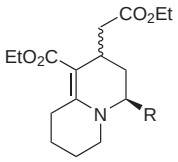
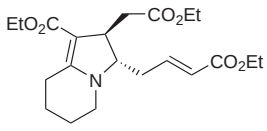
Entry	Iodide	Amine	Product	Yield (%)[b]
1	**1b**	**2a**	 **3a**: R = *i*-Pr	80
2	**1b**	**2b**	**3b**: R = Bn	76
3	**1b**	**2c**	**3c**: R = CH_2CO_2Et	65

Table 1 Reaction of Iodides **1** and Amines **2**[a] (continued)

Entry	Iodide	Amine	Product	Yield (%)[b]
4	**1b**	**2d**	 **3d**	64
5	**1a**	**2a**	 **3e**	51[c]
6	**1a**	**2d**	 **3f**	49[c]
7	**1b**	**2e**	 **3g**	85
8	**1b**	**2f**	 **3h**	74
9	**1b**	**2j**	 **3i**	90[d]
10	**1b**	**2h**	 **3j**: R = CH_2OBn	71[d]
11	**1b**	**2i**	**3k**: R = 3,4-$(MeO)_2C_6H_3$	85[d]
12	**1b**	**2g**	 **3m**	65

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), K_2CO_3 (0.7 mmol), 4 Å MS (40 mg) in 3 mL of MeCN, refluxed for 5–24 h.
[b] Isolated yield.
[c] Monocyclic product was isolated in about 30% yield.
[d] Ratio for *cis* and *trans* was about 1.5:1.

Notably, there was marked difference in yield between formation of **3a** and **3e** (compare entries 1 and 5), or **3d** and **3f** (compare entries 4 and 6). These results indicated that the second intramolecular Michael addition should be more difficult after formation of a five-membered ring than that of a six-membered ring. However, it seemed that a five-membered ring was easier to generate than a six-membered ring for the intramolecular Michael addition step because when **1b** reacted with **2g**, an amine bearing two α,β-unsaturated ester units, only indolizidine **3m**[5,8] was isolated (entry 12).

In conclusion, we have developed a novel cascade reaction process between ω-iodo-α,β-alkynoates and δ- or γ-amino α,β-unsaturated esters, which allowed the assembly of polysubstituted indolizidines, quinolizidines, and pyrrolizidines with a great diversity in a very efficient manner.[9] This method may find further application in the total synthesis of natural products and designed molecules for biological evaluation.

Acknowledgment

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References and Notes

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(2) Zhu, W.; Dong, D.; Pu, X.; Ma, D. *Org. Lett.* **2005**, *7*, 705.
(3) Zhu, W.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 5545.
(4) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149; and references cited therein.
(5) **General Procedure for Reaction of Iodides 1 with δ- or γ-Amino α,β-Unsaturated Esters 2:**
A mixture of **1** (0.22 mmol), **2** (0.23 mmol), anhyd K_2CO_3 (95 mg), and 4 Å MS (40 mg) in 3 mL of MeCN was refluxed until the starting materials disappeared as monitored by TLC. The cooled solution was concentrated and partitioned between brine and Et_2O. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified via chromatography to give **3**.
(6) Selected data for **3a**: $[\alpha]_D^{18}$ +138.0 (*c* 0.75, $CHCl_3$). IR (film): 1734, 1664, 1573 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.18–4.02 (m, 4 H), 3.28 (t, *J* = 3.6 Hz, 1 H), 3.22–3.18 (m, 1 H), 3.12–3.10 (m, 1 H), 3.03–2.99 (m, 1 H), 2.81 (dt, *J* = 18.0, 6.5 Hz, 1 H), 2.64 (dd, *J* = 14.0, 3.4 Hz, 1 H), 2.36 (dd, *J* = 14.0, 8.8 Hz, 1 H), 2.02–1.96 (m, 1 H), 1.82–1.61 (m, 5 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 0.88 (d, *J* = 8.7 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 166.7, 162.4, 161.2, 95.5, 73.2, 60.1, 58.1, 44.9, 40.7, 38.0, 24.8, 23.4, 20.0, 17.3, 15.8, 14.8, 14.4. MS: *m/z* = 323 [M^+]. ESI-HRMS: *m/z* calcd for $C_{18}H_{29}NO_4Na$: 346.1979 [M + Na]$^+$; found: 346.1989.
(7) Selected data for **3h**: $[\alpha]_D^{14}$ +53.6 (*c* 0.95, $CHCl_3$). IR (film): 2934, 1730, 1675, 1552 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 8 H), 7.12–7.10 (m, 2 H), 4.74 (d, *J* = 12.6 Hz, 1 H), 4.56 (d, *J* = 12.6 Hz, 1 H), 4.18–4.09 (m, 4 H), 3.74–3.73 (m, 1 H), 3.48 (d, *J* = 9.6 Hz, 1 H), 3.41–3.36 (m, 1 H), 3.28 (dt, *J* = 17.0, 5.0 Hz, 1 H), 3.07–2.99 (m, 1 H), 2.83–2.74 (m, 3 H), 2.61 (dd, *J* = 13.2, 4.7 Hz, 1 H), 2.52 (dt, *J* = 11.9, 5.0 Hz, 1 H), 2.38 (dd, *J* = 16.4, 11.0 Hz, 1 H), 1.69–1.64 (m, 1 H), 1.56–1.47 (m, 3 H), 1.29–1.19 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 169.2, 154.7, 139.0, 138.9, 129.0 (2 C), 128.5 (2 C), 128.3 (2 C), 127.4 (2 C), 127.3, 126.5, 93.0, 75.9, 70.1, 66.2, 60.2, 58.8, 52.6, 38.1, 36.9, 33.8, 27.8, 23.3, 20.5, 14.6, 14.3. MS (EI): *m/z* = 491 [M^+]. ESI-HRMS: *m/z* calcd for $C_{30}H_{37}NO_5Na$: 514.2586 [M + Na]$^+$; found: 514.2564.
(8) Selected data for **3m**: $[\alpha]_D^{18}$ –12.3 (*c* 0.5, $CHCl_3$). IR (film): 2930, 1728, 1665, 1574 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.88 (q, *J* = 7.5 Hz, 1 H), 5.90 (d, *J* = 15.5 Hz, 1 H), 4.22–4.03 (m, 6 H), 3.47 (q, *J* = 3.9 Hz, 1 H), 3.22–3.16 (m, 1 H), 3.09–2.96 (m, 2 H), 2.86–2.74 (m, 3 H), 2.52–2.47 (m, 2 H), 2.29 (dd, *J* = 15.6, 9.9 Hz, 1 H), 1.79–1.74 (m, 2 H), 1.65–1.59 (m, 2 H), 1.31–1.19 (m, 9 H). MS (EI): *m/z* = 393 [M^+]. ESI-HRMS: *m/z* calcd for $C_{21}H_{32}NO_6$: 394.2252 [M + H]$^+$; found: 394.2224.
(9) For some recent references for elaborating these molecules, see: (a) Epperson, M. T.; Gin, D. Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 1778. (b) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715. (c) Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Org. Lett.* **2002**, *4*, 1971. (d) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774. (e) Amos, D. T.; Renslo, A. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 4970. (f) Molander, G. A.; Pack, S. K. *J. Org. Chem.* **2003**, *68*, 9214. (g) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879. (h) Gracias, V.; Zeng, Y.; Desai, P.; Aubé, J. *Org. Lett.* **2003**, *5*, 4999. (i) Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 626. (j) Back, T. G.; Parvez, M.; Zhai, H. *J. Org. Chem.* **2003**, *68*, 9389. (k) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Chem. Eur. J.* **2003**, *9*, 3415. (l) Davis, F. A.; Yang, B. *Org. Lett.* **2003**, *5*, 5011. (m) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400. (n) Cassidy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029. (o) Poupon, E.; Francois, D.; Kunesch, N.; Husson, H. P. *J. Org. Chem.* **2004**, *69*, 3836. (p) Zech, G.; Kunz, H. *Chem. Eur. J.* **2004**, *10*, 4136. (q) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5219. (r) Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067. (s) Smith, A. B.; Kim, D. S. *Org. Lett.* **2004**, *6*, 1493. (t) Yu, S.; Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 7364.