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# An Efficient Sequential Reaction Process to Polysubstituted Indolizidines and Quinolizidines and Its Application to the Total Synthesis of Indolizidine 223A

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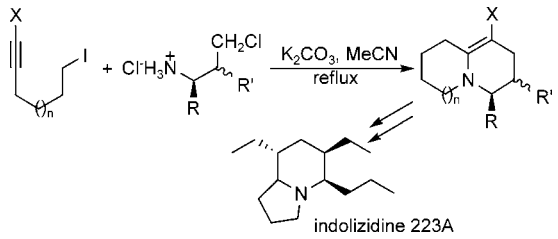
## ABSTRACT




**The reaction of iodides 1 with δ-chloropropylamines 5 in MeCN assisted with $K_2CO_3$ undergoes a sequential $S_N2$/Michael addition/$S_N2$/$S_N2$ reaction process to give polysubstituted indolizidines and quinolizidines. Using this method, indolizidine 223A is synthesized from 2-ethyl-2-hexenoic acid in 12 linear steps and 14.5% overall yield.**

There has been an increasing interest in developing novel transformations that rapidly evolve molecular complexity in a stereocontrolled fashion. One powerful approach toward this goal is to combine two or more distinct reactions into a single transformation, thereby producing a sequential reaction process.[1,2] During the studies aimed at synthesizing the indolizidine and quinolizidine alkaloids,[3] we have developed a sequential substitution/Michael addition/condensation reaction process[3a] to enantiopure quinolizidinones and indolizidinones **3** by refluxing enantiopure β-amino esters **2a** and iodides **1** in acetonitrile under the action of $K_2CO_3$ (Figure 1). Unfortunately, the efficiency of this process was greatly decreased by formation of a side product **4** through $H^+$ abstraction of intermediate **A**. This problem might result from lower reactivity of the ester moiety and therefore reaction of iodides **1** with δ-amino chlorides **2b** was considered. As a class of dipole building blocks, compounds **2b** have been employed by Back and Nakajima to assemble piperidines, indolizidines and quinolizidines by reacting with acetylenic sulfones.[4] However, in their work the N-containing heterocycles were obtained in a stepwise manner. In our case, it

(1) For a review, see: Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.

(2) For some recent references, see: (a) Cuny, G.; Bois-Choussy, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4774. (b) Tsuchii, K.; Doi, M.; Hirao, T.; Ogawa, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3490. (c) Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, N.; Yamada, K.; Muraoka, O.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1123. (d) Padwa, A.; Straub, C. S. *J. Org. Chem.* **2003**, *68*, 227. (e) Mauleon, P.; Nunez, A. A.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2003**, *9*, 1511.

(3) (a) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927. (b) Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503. (c) Ma, D.; Zhang, J. *Tetrahedron Lett.* **1998**, *39*, 9067.

(4) (a) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543.

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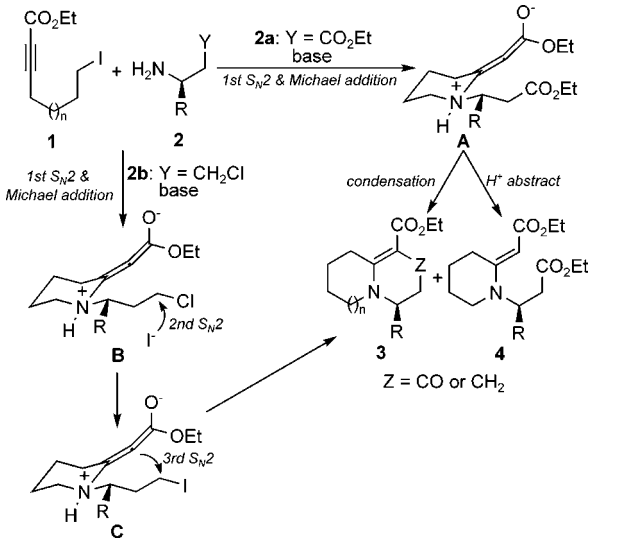



**Figure 1.** Possible reaction course of iodides **1** with $\beta$-amino esters or $\delta$-chloropropylamines **2**.

was expected that after the first attack of the amine moiety of **2b** to the terminal carbon of the iodide **1** and subsequent Michael addition to form the intermediate **B**, the resultant iodine anion would undergo a halogen exchange with the chloride, which in turn would generate a more reactive species to react with the enolate moiety as depicted in intermediate **C**, thereby avoiding the $H^+$ abstraction and giving bicyclic products exclusively.

With this idea in mind, a reaction of ethyl 6-iodo-2-hexynoate **1a** with 3-chloropropylamine hydrochloride **5a** was conducted in acetonitrile at 60 °C under the action of 3.5 equiv of $K_2CO_3$. We were pleased to notice that after 24 h indolizidine **6a** was isolated as a sole product in 92% yield (Table 1, entry 1). In view of this encouraging result, other iodides with different length of chain or electron-withdrawing groups and several substituted $\delta$-chloropropylamines **5b**−**5h** were explored for this sequential reaction process. It was found that in most cases substituted indolizidine (entries 2 and 3), quinolizidine (entries 4−6), or even piperidinoazpine ring (entry 7) products were isolated in good yields. Noteworthy is that several electron-withdrawing groups of iodides **1** such as carboxylate ester, tosyl, and phosphonate are compatible with this process and are ready for further transformations to natural products.[4,5] In addition, successful formation of **6b** and **6e** indicated that halogen exchange should be necessary for closure of the second ring because in a similar case,[4] addition of $\delta$-chloropropylamines to acetylenic sulfones in several refluxed solvents did not give any cyclization products directly.

To further explore the scope of this sequential reaction process, several enantiopure α-substituted or α,$\beta$-disubstituted $\delta$-chloropropylamines **5b**−**5d** were assembled.[6] It was found that all of these substrates worked for this process to provide corresponding polysubstituted indolizidines and quinolizidines although higher reaction temperature was required in comparison with **5a** (entries 8−11).

When ynone-derived iodide **1g** was used, only direct Michael addition product was isolated (entry 12), which indicated that ynone moiety of **1g** was the target for first attack. This result implied that its ynone part was more reactive than its terminal iodide part. However, this priority was also dependent on the nature of nucleophiles because when **1g** reacted with sterically hindered α-substituted $\delta$-chloropropylamine **5d**, the desired product **6n** was obtained in 55% yield although about 20% direct Michael addition product was still isolated (entry 13). It was known that Michael addition of LDA to the α,$\beta$-unsaturated ester of methyl 6-bromo-2-hexenoate or methyl 2-heptenoate could initiate the ring closure.[7] However, in our case no ring closure products through the direct Michael addition products were determined, which might result from quick $H^+$ abstract of the generated carbanion.

On the basis of the above investigations, we next developed a concise synthesis of indolizidine 223A (**14**)[8] as outlined in Scheme 1. The synthesis started from **8**, an enantiopure $\beta$-amino ester that was prepared from a commercial available acid **7** in two steps and 67% yield based on the procedure of Davies.[8c,9] Reduction of **8** with LAH afforded $\delta$-amino alcohol **9**, which was exposed to $SOCl_2$, followed by $Pd(OH)_2$/C-catalyzed hydrogenolysis to provide $\delta$-chloropropylamine hydrochloride **10**. Next, heating a mixture of **10**, **1a**, $K_2CO_3$ and 4 Å MS in MeCN delivered indolizidine **11** in 80% yield. Hydrogenation of **11** under the catalysis of $PtO_2$ worked well to produce a mixture of 8$\beta$-isomer **12a** and 8α-isomer **12b**. This reaction should give **12a** initially and then form **12b** through C8 epimerization, which was proved by complete conversion to **12b** through treatment of the above mixture with sodium ethoxide. The stereochemistry of **12b** was assigned by NOESY studies and the overall yield was 75% from **11**. Finally, reduction of **12b** produced alcohol **13**, which was oxidized to give an aldehyde. Wittig reaction of this aldehyde followed by hydrogenation furnished **14**. Its analytical data were all-identical with those reported.[8] This protocol consists of 12 linear steps from **7** in 14.5% overall yield, representing the most efficient one for synthesizing indolizidine 223A to date.

Alkaloids incorporating the indolizidine and quinolizidine skeletons comprise a rather large class of compounds isolated from diverse natural sources.[10] These natural products displayed a considerable range of biological activity including

(5) For other emerging examples, see: (a) Haddad, M.; Celerier, J.-P.; Lhommet, G. *Heterocycles* **1987**, *26*, 2335. (b) Michael, J. P.; Gravestock, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1919. (c) Bates, R. W.; Boonsombat, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 654.

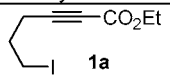
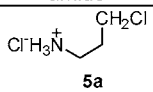
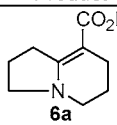
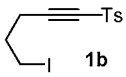
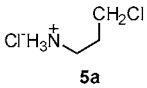
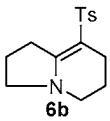
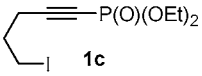
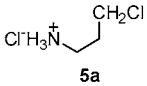
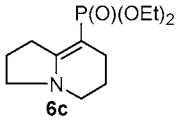
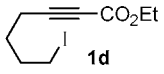
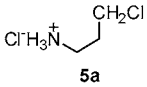
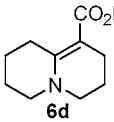
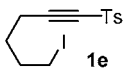
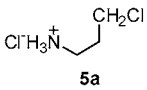
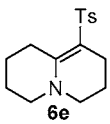
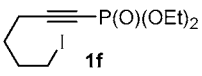
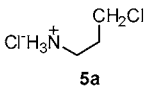
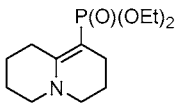
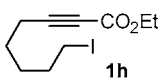
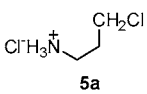
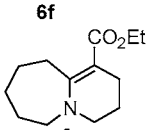
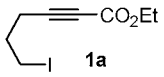
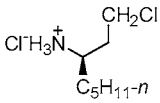
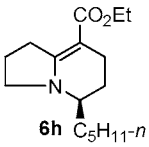
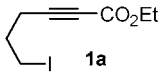
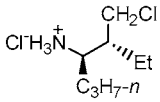
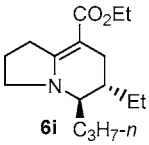
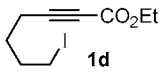
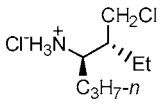
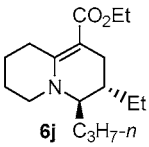
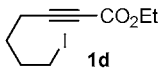
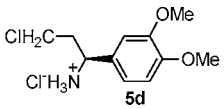
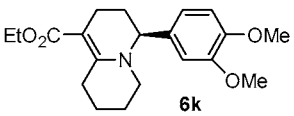
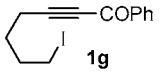
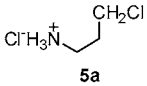
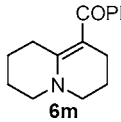
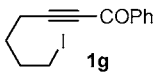
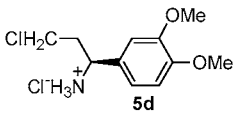
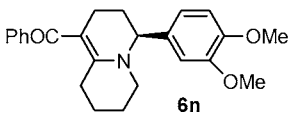
(6) They were prepared from corresponding $\beta$-amino esters (see refs 3a and 7c) following a procedure from **9a** to **10**.

(7) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609.

(8) Isolation: (a) Garraffo, H. M.; Jain, P.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **1997**, *60*, 2. For synthesis of indolizidine 223A and its epimer, see: (b) Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715. (c) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400. (d) Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371.

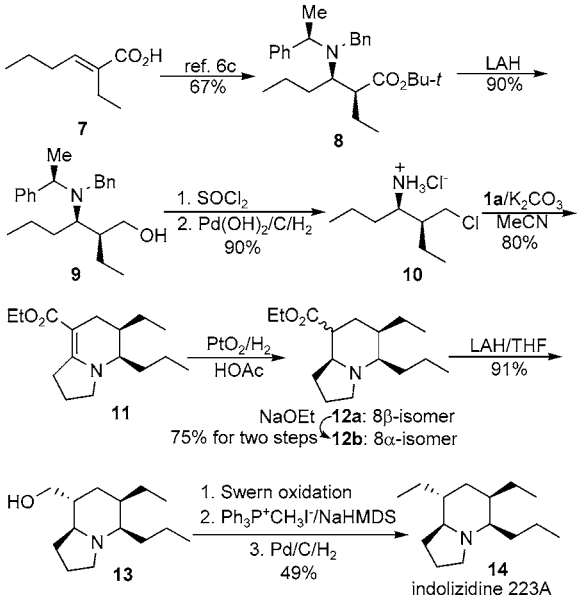
(9) Davies, S. G.; Ichihara, O.; Walters, I. S. *J. Chem. Soc., Perkin Trans 1* **1994**, 1141.

**Table 1.** Reaction of Iodides **1** with δ-Chloropropylamines **5**[a]

| entry | vinyl halide | amide | temp. (°C)/ time (h) | Product | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  **1a** |  **5a** | 60/24 |  **6a** | 92 |
| 2 |  **1b** |  **5a** | 82/24 |  **6b** | 87 |
| 3 |  **1c** |  **5a** | 82/36 |  **6c** | 84 |
| 4 |  **1d** |  **5a** | 65/36 |  **6d** | 81 |
| 5 |  **1e** |  **5a** | 82/18 |  **6e** | 83 |
| 6 |  **1f** |  **5a** | 82/48 |  **6f** | 70 |
| 7 |  **1h** |  **5a** | 70/24 |  **6g** | 62 |
| 8 |  **1a** |  **5b** | 82/24 |  **6h** $C_5H_{11}$-*n* | 80 |
| 9 |  **1a** |  **5c** | 82/36 |  **6i** $C_3H_7$-*n* | 70 |
| 10 |  **1d** |  **5c** | 82/24 |  **6j** $C_3H_7$-*n* | 75 |
| 11 |  **1d** |  **5d** | 82/48 |  **6k** | 63 |
| 12 |  **1g** |  **5a** | 30-60/24 |  **6m** | 0[c] |
| 13 |  **1g** |  **5d** | 30-60/24 |  **6n** | 55[d] |

[a] Reaction conditions: **1** (0.2 mmol), **5** (0.2 mmol), $K_2CO_3$ (0.7 mmol), and 4 Å MS (40 mg) in 3 mL of MeCN, reflux. [b] Isolated yield. [c] Direct Michael addition product was isolated in 80% yield. [d] Direct Michael addition product was isolated in 20% yield.

**Scheme 1**




neurological and antitumor functions. These features make them one of the most popular targets for organic synthesis.[10,11] The present sequential reaction processes, giving enantiopure polysubstituted indolizidines and quinolizidines in a very efficient manner, should find further application in the total synthesis of natural products, as well as diversity-oriented synthesis for drug development and chemical biology.[12]

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**Supporting Information Available:** Experimental procedures and characterization for compounds **6**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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