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A short and convenient synthesis of chiral heterocyclic β-enamino esters from halogeno acetylenic esters

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Abstract—An efficient synthesis of chiral pyrrolidine and piperidine enamino esters is described in one step from methyl halogeno alcynoate and (*S*)-1-phenylethylamine or (*S*)-phenylglycinol.

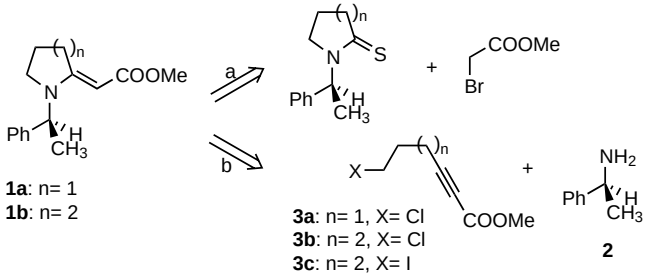
Heterocyclic trisubstituted enamino esters have found broad interest in the synthesis of various natural products such as indolizidine alkaloids,[1] (±)-prosopinine,[2] (±)-lythrancepines II and III,[3] (+) and (−)-anatoxin *a*,[4] and (±)-gephyrotoxin.[5] Enamino ester intermediates are next acylated or alkylated, but more often directly reduced. For our part, in short earlier papers, we described a versatile access to pyrrolizidine,[6] indolizidine[7] and quinolizidine[6] alkaloids using a reduction–alkylation sequence on the enamino esters **1a** and **1b**.[8,9] In all cases, the strategy adopted to prepare the appropriate enamino esters was the elegant Eschenmoser sulfide contraction procedure.[10]

However, difficulties, probably due to phosphorus and sulfur residues, were encountered by us and others[11] during either the catalytic hydrogenation of the trisubstituted double bond of the enamino ester, or the debenzylation step. In order to obtain reproducible results, several chromatographies and recrystallization were sometimes necessary, considerably reducing the yields.

In relation to our synthetic investigations utilizing the chiral enamino esters **1a** and **1b** prepared through the Eschenmoser reaction[12] (Scheme 1, route a), we sought an alternative process by way of which the phosphorus-containing reagents could be avoided.

In order to obtain *N*-substituted pyrroles, Bryson[13] reported a relatively simple preparation of pyrrolidine enamino esters by concomitant Michael addition–alkylation of primary aliphatic or aromatic amines with methyl 6-chlorohexynoate **3a**, in the presence of sodium iodide and sodium carbonate. Thereby, we thought that chiral enamino esters **1a** and **1b** could be easily prepared by this method directly from the appropriate methyl halo alcynoates **3** and chiral amine **2** (Scheme 1, route b).

Recently, Ma and Zhu described a total synthesis of (−)-lasubine II[14] following this same strategy to build their appropriate enamino esters from halo alcynoates and various amines. These results prompt us to publish in preliminary form our findings about the reactivity of halogeno acetylenic carboxylates with chiral amines. In this communication we describe a new synthesis of pyrrolidine and piperidine enamino esters by reaction of halogeno acetylenic esters with enantiopure phenylethylamine and phenylglycinol.



Scheme 1.

Keywords: pyrrolidine; piperidine; enamino ester; acetylenic ester; chiral amine.

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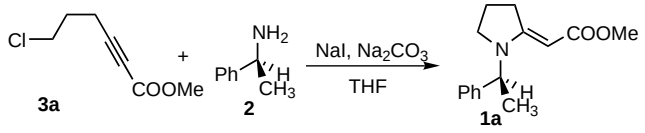
Results and discussion

We first examined the preparation of the pyrrolidine enamino ester **1a** through this attractive methodology. In a typical procedure (Scheme 2), an equimolar mixture of (*S*)-1-phenylethylamine **2** and methyl 6-chlorohexynoate **3a**,[15] in the presence of sodium iodide (1 equiv.) and sodium carbonate (2 equiv.) was heated in refluxing THF for 3 days. Simple acid–base workup gave quantitatively **1a**[16] in almost pure form, as a sole (*E*)-isomer; thus, it can be used directly in the following reduction step.

Encouraged by these results, we then extended our study to the synthesis of the piperidine enamino ester **1b** in order to improve the scope and synthetic utility of this strategy. However, when (*S*)-1-phenylethylamine **2** was condensed with methyl 7-chloroheptynoate **3b**,[17] in the conditions described above (Scheme 3 and Table 1, entry 2), the undesired cyclohexene **4** was obtained along with the expected enamino ester **1b** in 55/45 ratio.

This result could be explained considering two different mechanistic routes.[18]



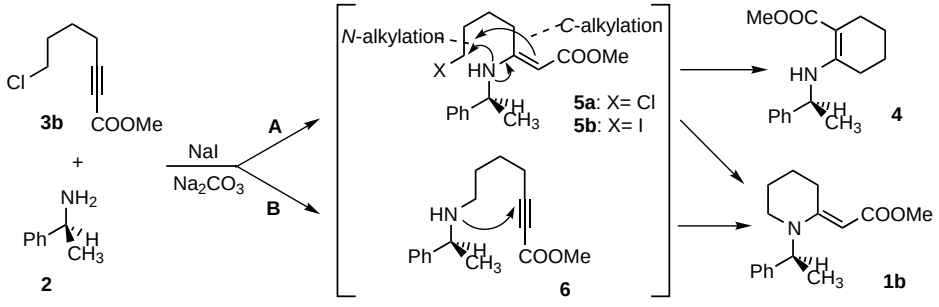
Scheme 2.

Route **A** involves the acyclic enamine intermediate **5** firstly formed by Michael addition of the (*S*)-1-phenylethylamine to activated acetylenic bond of **3b**. Enamine **5** could then react according to two different pathways: *N*-alkylation led to exocyclic enamino ester **1b** while *C*-alkylation provided **4**.

In route **B**: halide substitution of alcynoate **3b** by chiral amine could lead to compound **6** which then evolves only towards enamino ester **1b** through intramolecular Michael addition.

We then reconsidered the conditions described by Bryson in order to decrease or eliminate the formation of **4**. The various conditions examined were reported in Table 1.

The reaction was first performed in different solvents, without adjunction of NaI. Non-polar solvents (toluene or xylene) were not suitable because a complex mixture was produced, or no reaction occurred in these cases (entries 4 and 5). The use of a polar solvent such as DMF led to a complete consumption of starting materials, but **4** was still the major product in the mixture (entry 6) while in THF or CH_3CN the reaction was not even complete after 15 days under reflux (entries 1 and 7); however CH_3CN led to a better result, since the yield of enamino ester increased up to 70%. In a higher boiling point solvent such as *n*-BuCN (entry 9), the reaction was complete in 6 days but furnished an equimolar mixture of **1b** and **4**. It is noteworthy that

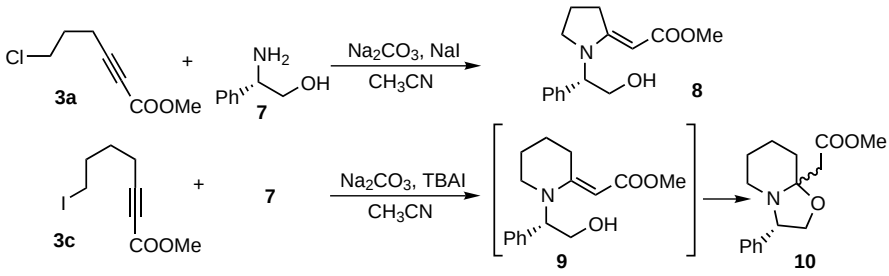


Scheme 3.

Table 1. Reaction of methyl 7-chloroheptynoate **3b** with (*S*)-1-phenylethylamine **2**[a]

Entry	Refluxing solvent	NaI (equiv.)	Time (days)	Ratio (%)[b] **1b**/**4**	
1	THF	–	15	50	50[c]
2	THF	1	7	45	55
3	THF	3	3	40	60
4	Toluene	–	3	No reaction	
5	Xylene	–	4	Complex mixture	
6	DMF	–	2	30	70
7	CH_3CN	–	15	70	30[c]
8	CH_3CN	1	6	65	35
9	*n*-BuCN	–	6	50	50
10	None	–	–[d]	0	100

[a] All experiments were realized in the presence of Na_2CO_3 as base, until complete consumption of **3b**.
[b] The ratio **1b**/**4** was determined by GC and ^1H NMR spectrum of crude product.
[c] Unreacted amine: ~30%.
[d] Reaction conditions: $T=120°C$, 30 min.



Scheme 4.

the sole product **4**[19] was obtained when the reactants were rapidly heated at 120°C without solvent (entry 10).

Next, we studied the influence of various quantities of sodium iodide in order to convert, in situ, methyl 7-chloroheptynoate **3b** into the iodo derivative **3c**. We attempted to increase the attack of primary amine at the halo substituted carbon of the iodo alcynoate **3c**, leading to the amino alcynoate **6** and thus favoring route **B**. However, entries 1–3 (in THF) and entries 7 and 8 (in CH_3CN) showed that the adjunction of 1 to 3 equiv. of NaI reduced the reaction time, but favored the formation of the cyclohexene **4**, which is not in agreement with this hypothesis.

In view of this paradox, we checked that the halogen exchange reaction of **3b** into **3c** by means of NaI was slow (>3 days) with regard to the amine addition to acetylenic ester bearing a simple alkyl chain (24 h). Thus, we assumed that there was a rapid accumulation of the Michael adduct **5a** which then underwent the halogen exchange, leading to the corresponding iodo enamine **5b**. Cyclization of this preferentially furnished the cyclohexene **4**. This can be explained by considering the relative hardness and softness of the enamine reactive centers versus the halide moiety in the intramolecular substitution. The nitrogen atom of enamine is known to be a hard center while its carbon atom is considered as a soft one. So, in the case of the enamine **5a** which possesses a chlorine atom (hard), *N*-alkylation is favored while the corresponding compound **5b** bearing a iodine atom (soft), gives rise preferentially to *C*-alkylation.

This study by varying experimental conditions did not allow us to form the enamino ester **1b** from methyl 7-chloroheptynoate with a good selectivity. So we decided to engage in reaction directly methyl 7-iodoheptynoate **3c**.[20] This compound was prepared from methyl 7-chloroheptynoate **3b** in boiling acetone in the presence of 4 equiv. of sodium iodide. The reaction between methyl 7-iodoheptynoate **3c** and (*S*)-1-phenylethylamine was complete in 4 days (Na_2CO_3, refluxing CH_3CN) and afforded the expected enamino ester **1b** accompanied by only 5% of the cyclohexene **4**. We found that the addition of a catalytic amount of tetrabutylammonium iodide reduced the reaction time (2 days) and led to the exclusive formation of **1b** (*E*-isomer) in 95% yield.[21]

This method was successfully applied to (*S*)-phenylglycinol **7**. Thus methyl 6-chlorohexynoate **3a** in refluxing CH_3CN provided the enamino ester **8** (*E*-isomer) in 95% yield.[8a,22]

When methyl 7-iodoheptynoate **3c** was put in reaction with (*S*)-phenylglycinol in the conditions used for **1b**, the expected enamino ester **9** was not observed (Scheme 4). In place, we isolated the bicyclic derivative **10** in 90% yield.[23] This compound obtained as a mixture of two diastereomers in a 90:10 ratio, is issued from the intramolecular addition of the hydroxymethyl moiety of **9** to its enamine double bond.

In conclusion, this procedure for preparing chiral heterocyclic enamino esters proceeds in a high overall yield and provides an alternative to the excellent procedure of Eschenmoser with the operational advantages that phosphines need not be employed and that only one step is required from the chiral amines to enamine targets. Therefore, this approach minimized the loss of chiral starting material.[12] Thus, our preparation of **1** would improve the total syntheses of pyrrolizidine, indolizidine and quinolizidine alkaloids we recently realized.[6,7]

We are currently investigating this approach to further highly functionalized enamines synthesis, as well as applications to biologically significant polycyclic alkaloids.

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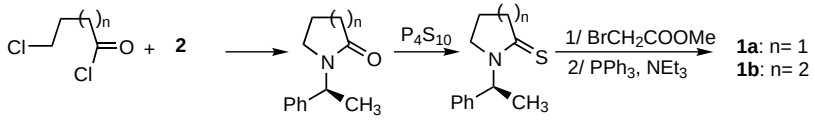
References

1. (a) Michael, J. P.; Gravestock, D. *Eur. J. Org. Chem.* **1998**, 865–870; (b) Michael, J. P.; Gravestock, D. *Synlett* **1996**, 981–982.
2. Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669–1672.
3. Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1987**, *52*, 4665–4673.

4. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539–4547.
5. Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255–1263.
6. Ledoux, S.; Marchalant, E.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **2001**, *42*, 5397–5399.
7. Bardou, A.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1998**, *39*, 5189–5192.
8. (a) Nikiforov, T.; Stanchev, S.; Milenkov, B.; Dimitrov, V. *Heterocycles* **1986**, *24*, 1825–1829; (b) Bardou, A.; Célérier, J.-P.; Lhommet, G. *Tetrahedron Lett.* **1997**, *38*, 8507–8510.
9. Ledoux, S. Ph.D. Thesis, Université P. and M. Curie, Paris, **2000**.
10. (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710–734; (b) Shiosaki, K. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; pp. 865–892.
11. Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313–6325.
12. Synthesis of **1a**[8] and **1b**[9] through Eschenmoser condensation:



13. Wilson, C. A., II; Bryson, T. A. *J. Org. Chem.* **1975**, *40*, 800–801.
14. Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927–3929.
15. Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216–7227.
16. Capillary gas chromatography of the crude product showed 98% of **1a**. For the (*E*)-stereochemistry of the double bond, see Ref. 10b, p. 872. Flash chromatography gave pure **1a** in 95% yield. Selected data: ^{1}H NMR 250 MHz ($CDCl_3$) δ (ppm): 1.53 (d, 3H, $J=7$ Hz); 1.70–2.00 (m, 2H); 3.06–3.34 (m, 4H); 3.60 (s, 3H); 4.65 (s, 1H); 4.85 (q, 1H, $J=7$ Hz); 7.15–7.34 (m, 5H). ^{13}C NMR 62.9 MHz ($CDCl_3$) δ (ppm): 16.8; 20.9; 32.8; 47.2; 49.9; 52.9; 77.9; 126.5; 127.4; 128.6; 140.4; 164.9; 169.9. $[\alpha]_D^{20}$ −256 (*c* 1.1, EtOH) mp 71°C. Anal. calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.70. Found: C, 73.56; H, 7.93; N, 5.57.
17. Compound **3b** was prepared in quantitative yield from 6-chlorohex-1-yne as described for **3a** in Ref. 15. Selected data for **3b**: ^{1}H NMR 250 MHz ($CDCl_3$) δ (ppm): 1.72–1.80 and 1.85–1.94 (2m, 4H); 2.40 (t, 2H, $J=7.0$ Hz); 3.56 (t, 2H, $J=6.2$ Hz); 3.76 (s, 3H). ^{13}C NMR 62.9 MHz ($CDCl_3$) δ (ppm): 17.4; 24.4; 31.0; 43.8; 52.0; 72.9; 88.0; 153.4.
18. (a) Bunce, R. A.; Peeples, C. J.; Jones, P. B. *J. Org. Chem.* **1992**, *57*, 1727–1733; (b) Bunce, R. A.; Allison, J. C. *Synth. Commun.* **1999**, *29*, 2175–2186.
19. For spectral data of **4**, see: Cavé, C.; Daley, V.; d'Angelo, J.; Guingant, A. *Tetrahedron: Asymmetry* **1995**, *6*, 79–82.
20. For spectral data of **3c**, see: Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Taniguchi, M.; Kondo, M.; Sasho, M. *J. Org. Chem.* **1991**, *56*, 119–125.
21. For the (*E*)-stereochemistry of the double bond, see Ref. 10b, p. 872. Selected data for **1b**: ^{1}H NMR 250 MHz ($CDCl_3$) δ (ppm): 1.52 (d, 3H, $J=7$ Hz); 1.61–1.65 (m, 4H); 2.78–2.9 (m, 1H); 2.92–3.08 (m, 1H); 3.12–3.31 (m, 2H); 3.60 (s, 3H); 4.87 (s, 1H); 5.12 (q, 1H, $J=7$ Hz); 7.23–7.34 (m, 5H). ^{13}C NMR 62.9 MHz ($CDCl_3$) δ (ppm): 15.6; 19.7; 23.3; 26.7; 42.3; 50.3; 55.6; 81.8; 127.3; 127.7; 128.9; 142.1; 165.1; 171.6. $[\alpha]_D^{20}$ −121 (*c* 1.10, CH_2Cl_2), mp 52°C. Anal. calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.99; H, 8.00; N, 5.27.
22. For the (*E*)-stereochemistry of the double bond, see Ref. 10b, p. 872. Selected data for **8**: ^{1}H NMR 250 MHz ($CDCl_3$) δ (ppm): 1.67 (t, 1H); 1.93–2.04 (m, 2H); 3.22 (m, 2H); 3.32–341 (m, 1H); 3.51–3.61 (m, 1H); 3.58 (s, 3H); 4.05–4.11 (m, 2H); 4.66 (s, 1H); 4.79 (t, 1H, $J=6.2$ Hz); 7.19–7.39 (m, 5H). ^{13}C NMR 62.9 MHz ($CDCl_3$) δ (ppm): 21.1; 32.7; 48.3; 50.1; 60.3; 62.6; 78.6; 127.0; 127.9; 128.9; 136.7; 166.1; 170.1. $[\alpha]_D^{20}$ +224 (*c* 1.18, $CHCl_3$), mp 61°C. Anal. calcd for $C_{15}H_{21}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.07; H, 7.39; N, 5.29.
23. Absolute configurations of the two isomers of **10** could not be assigned. Selected data for the major diastereomer **10**: ^{1}H NMR 250 MHz ($CDCl_3$) δ (ppm): 1.17–1.24 (m, 2H); 1.42–1.84 (m, 4H); 2.5–2.98 (m, 4H); 3.61–3.71 (m, 1H); 3.75 (s, 3H); 4.18–4.26 (m, 1H); 4.32–4.39 (m, 1H); 7.26–7.36 (m, 5H). ^{13}C NMR 62.9 MHz ($CDCl_3$) δ (ppm): 18.4; 21.9; 31.1; 41.4; 42.4; 51.3; 62.2; 72.9; 93.4; 127.5; 127.6; 128.0; 128.3; 139.4; 170.5. Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.68; N, 5.08. Found: C, 69.82; H, 7.73; N, 5.02.