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Easy Access to α-Amino β-Oxo Esters from β-Enamino Esters

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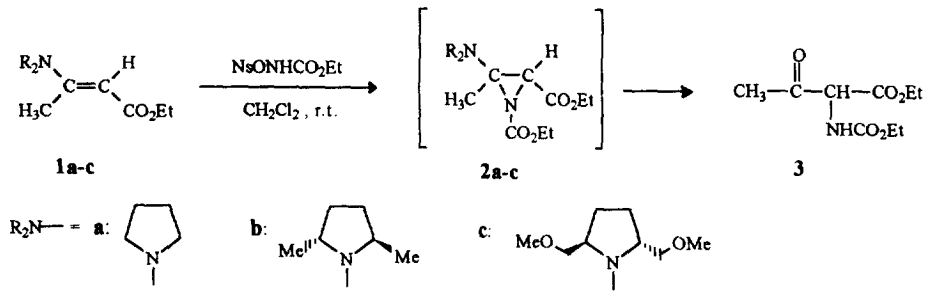
Abstract: *N*-Substituted α-amino β-oxo esters have been obtained by amination of β-enamino esters with ethyl *N*-[(4-nitrobenzenesulphonyl)oxy]carbamate ($NsONHCO_2Et$), in the absence of added bases. The use of optically active pyrrolidines with C_2 symmetry as chiral auxiliaries induces diastereoselectivities up to 80%.

Keywords: Amination; Amino acids and derivatives.

In the course of our studies on the amination reactions with ethyl [(arenesulphonyl)oxy]carbamates ($ArSO_3NHCO_2Et$),[1] we have tested different substituted alkenes, bearing electron-donating[2] or electron-withdrawing groups.[3] We became interested in considering the amination reaction of typical "push-pull" alkenes, chiral β-enamino esters (vinylogous carbamates)[4] derived from pyrrolidines with C_2 symmetry, the chiral auxiliaries recently used by us to successfully aminate cyclopentanone enamines.[5] Similar chiral β-enamino esters are known to give high asymmetric induction in alkylation reactions.[6]

In this paper we report the first results obtained on reacting ethyl *N*-[(4-nitrobenzenesulphonyl)oxy]carbamate ($NsONHCO_2Et$)[7] with the β-enamino esters **1a-c** to give ethyl 2-[(ethoxycarbonyl)amino]-3-oxobutanoate (**3**), a precursor of potentially bioactive α–amino β–hydroxy acids.[8]



The amination reactions were performed using a molar excess of $NsONHCO_2Et$ in CH_2Cl_2 at room temperature. In all cases we detected by GC-MS an intermediate, possibly the aziridines **2a-c**, whose spontaneous hydrolysis during the reaction gave **3**.

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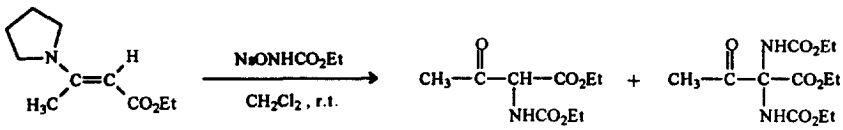
We started our study by testing the reaction of **1a** in the presence of an organic (Et_3N) or inorganic base (CaO) and in the absence of an added base.[9] After work-up either triethylammonium or calcium or pyrrolidinium nosylate was obtained. In the last case after hydrolysis it was possible to recover the starting amine; this is an important feature mainly when chiral amines are used as starting materials. The results are reported below.

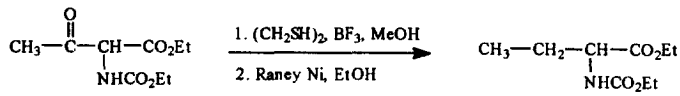


1a **3** **4**

Base	Molar ratio 1a:NsONHCO$_2$Et:base	Reaction time (h)	Yield (%) 3	Yield (%) 4
CaO	1:2:1	48	26	8
Et_3N	1:3:3	14	18	5
-	1:1	45	40	-

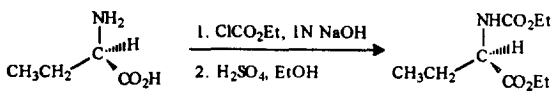
As shown above, the amination reaction performed in the presence of an added base gave the undesired bis-functionalised product **4**, probably resulting from the deprotonation of **3** at the α position.[10] On the contrary, in the reaction carried out in the absence of added bases **3** was obtained as a single product in better yield.[11]

We chose the last reaction conditions to obtain optically active α-amino β-oxo esters, starting from the chiral β-enamino esters **1b** and **1c**. The configuration of the major enantiomer was determined by conversion of the enantio-enriched mixture of **3** into the enantio-enriched mixture of **5**: the mixture of **5** is dextrorotatory ($[\alpha]_D$ +2.1; c = 0.6, in $CHCl_3$) for the reaction products coming from **1b** and laevorotatory ($[\alpha]_D$ -2.3; c = 0.7, in $CHCl_3$) for those coming from **1c**.[12]



3 **5**

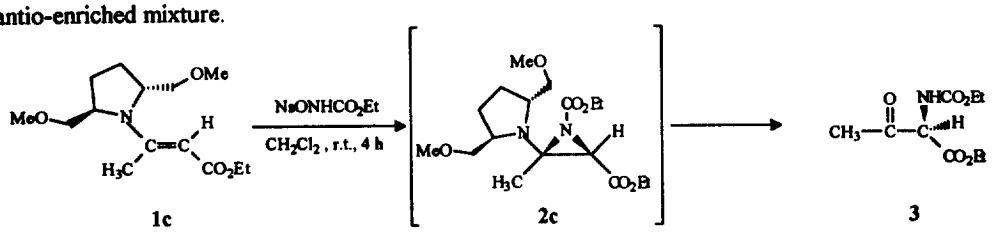
In this way, the knowledge of the optical rotation of ethyl (*R*)-(-)-2-(ethoxycarbonylamino)butanoate (**5**),[13] synthesised from the commercial D-α-aminobutyric acid (**6**), allowed us to assign the *S* configuration to the major enantiomer of **3** obtained from **1b** and the *R* configuration to that obtained from **1c**.



D-6 **(*R*)-5**

Furthermore, with the aim of knowing the degree of asymmetric induction from these aminations, we attempted to isolate the unstable intermediate mixture of diastereomeric aziridines, the only experimental evidence of which rests on GC-MS analysis. Starting from **1c**, the reaction conditions were modified by using equimolar amounts of substrate and NsONHCO$_2$Et and a shorter reaction time (4 h). In these conditions, it was possible to determine the diastereomeric excess (80%) of **2c** by GC and HPLC analyses of the crude mixture.

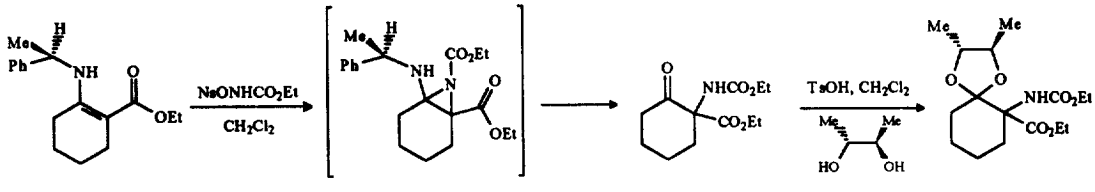
After HPLC purification it was possible to isolate an intermediate,[14] that hydrolysed very quickly to give **3** as an enantio-enriched mixture.



1c **2c** **3**

major diastereomer (80% d.e.) major enantiomer

Considering the great interest in asymmetric synthesis of optically active compounds containing quaternary carbon centres,[15] the amination reaction was attempted on the chiral β-enamino ester **7**,[16] derived from commercially available (*R*)-1-phenylethylamine and 2-(ethoxycarbonyl)cyclohexanone.



7 **8** **9** (60% d.e.)

In a first experiment, 2-(ethoxycarbonyl)-2-(ethoxycarbonylamino)cyclohexanone (**8**) was obtained in 49% yield. The enantiomeric excess was estimated by conversion of **8** into the corresponding diastereomeric ketals **9** (95% yield, 60% d.e.).[5,17]

As the mechanism is concerned, the available data do not allow us to indicate whether (ethoxycarbonyl)nitrene adds to the double bond or a conjugate addition occurs.[1,3] However, while preliminary attempts to obtain the same products from **1a** and **7** by N_3CO_2Et photolysis failed, further studies are under way.

Synthesis of ***1a-c.*** To a solution of 10 mmol of ethyl 2-butynoate (*Fluka*) in 10 ml of *tert*-butyl alcohol, 10 mmol of pyrrolidine (*Merck*), (2*R*,5*R*)-2,5-dimethylpyrrolidine[18] or (2*R*,5*R*)-2,5-bis(methoxymethyl)pyrrolidine (*Fluka*) was added at room temperature. The mixtures were refluxed for 4 h, 7 h and 30 h, respectively; after solvent evaporation, the β-enamino esters **1a-c** were obtained in good yields (90-95%) and characterised.[19]

Amination Reactions with NsONHCO₂Et. To a stirred solution of 5 mmol of β-enamino ester in 10 ml of CH_2Cl_2, NsONHCO₂Et (5 mmol for **1a**, 7 mmol for **1b**, 10 mmol for **1c** and 15 mmol for **7**) was added batchwise at room temperature. After 2 d of stirring, petroleum ether was added and nosylate salt was filtered. After evaporation of the solvent, the *N*-substituted α-amino β-oxo esters were separated by flash chromatography on silica gel (hexane/ethyl acetate, 7:3) and characterised.[20]

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11. The substrate itself or alternatively traces of pyrrolidine either present or formed in the reaction medium could act as the base.
12. The filtered crude mixture of **3** was reduced into **5** and then purified by flash chromatography (hexane/ethyl acetate, 9:1).
13. (*R*)-**5**: $[\alpha]_D$ - 4.75 (*c* = 0.18 in $CHCl_3$); IR (CCl_4) 3439, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (*t*, 3 H, CH_3), 1.21 (*t*, 3 H, OCH_2CH_3), 1.24 (*t*, 3 H, OCH_2CH_3), 1.52-1.96 (*m*, 2 H, CH_2), 4.09 (*q*, 2 H, CH_2O), 4.16 (*q*, 2 H, CH_2O), 4.20-4.33 (*m*, 1 H, CHN); 5.22-5.38 (*br*, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 9.35, 14.08, 14.44, 25.78, 54.78, 60.97, 61.19, 156.10, 172.49; GC-MS *m/z* 203 (M^+, 0.14), 130 (100), 102 (10), 86 (14), 58 (68), 56 (14), 41 (13).
14. Whose spectral data might suggest the aziridine **2c**: IR (CCl_4) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (*s*, 3 H, CH_3), 1.20-1.36 (*m*, 6 H, CH_2CH_3), 1.82-2.14 (*m*, 4 H, ring CH_2), 2.39 (*s*, 1 H, $CHCO_2$), 3.28 (*s*, 6 H, CH_3), 3.04-3.48 (*m*, 6 H, CH_2O, HCN), 4.05-4.19 (*m*, 4 CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 13.92, 14.28, 14.48; 26.07, 31.51, 58.67, 59.00, 59.79, 61.21, 72.81, 73.55, 156.21, 168.12; GC-MS *m/z* 358 (M^+, 9), 313 (49), 268 (12), 267 (79), 193 (12), 184 (40), 163 (10), 135 (17), 111 (26), 109 (13), 81 (15), 79 (16), 75 (24), 71 (100), 68 (43), 55 (12), 45 (48), 41 (27), 29 (35).
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17. **9**: IR (CCl_4) 3412, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (*d*, 3 H, CH_3), 1.00 (*d*, 3 H, CH_3), 1.12-2.16 (*m*, 13 H, CH_3, CH_2, *H*CHCO), 2.95-3.10 (*m*, 1 H, HC*H*CO), 3.27-3.42 (*m*, 1 H, C*H*CH_3), 3.57-3.73 (*m*, 1 H, C*H*CH_3), 4.03-4.25 (2*q*, 4 H, OCH_2CH_3), 5.06-5.22 (*br*, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 14.12, 14.21, 14.55, 15.99, 17.20, 20.08, 22.48, 22.69, 23.43, 25.19, 26.38, 29.36, 29.64, 31.92, 32.18, 34.58, 60.80, 61.24, 62.82, 78.33, 78.73, 79.34, 79.73, 107.71, 107.92, 155.01, 168.05; GC-MS *m/z* 329 (M^+, 7), 128 (10), 127 (100), 114 (54), 101 (11), 82 (10), 55 (35).
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19. **1a**: IR (CCl_4) 1693, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (*t*, 3 H, CH_2CH_3), 1.80-1.85 (*m*, 4 H, ring CH_2), 2.35 (*s*, 3 H, CH_3), 3.0.1-3.19 (*m*, 4 H, CH_2N), 3.97 (*q*, 2 H; OCH_2), 4.35 (*s*, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 14.67, 16.59, 25.11, 47.81, 57.99, 83.18, 159.49, 169.15; GC-MS *m/z* 183 (M^+, 39), 154 (62), 139 (10), 138 (100), 111 (51), 110 (89), 83 (80), 82 (16), 70 (65), 69 (22), 68 (33), 67 (13), 55 (24), 43 (19), 42 (32), 41 (52).
1b: $[\alpha]_D$ +187.8 (*c* = 1.3 in CH_2Cl_2); IR (CCl_4) 1686, 1573 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (*d*, 6 H, CH_3), 1.34 (*t*, 3 H, CH_2CH_3), 1.52-1.61 (*m*, 2 H, ring CH_2), 2.12-2.25 (*m*, 2 H, ring CH_2), 2.48 (*s*, 3 H, CH_3), 3.88-4.19 (*m*, 4 H OCH_2, CHN), 4.51 (*s*, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 14.78, 17.10, 29.91, 54.21, 58.08, 86.06, 158.19, 169.26; GC-MS *m/z* 211 (M^+, 24), 196 (17), 183 (12), 182 (100), 166 (51), 138 (19), 110 (14), 98 (16), 97 (14), 96 (36), 85 (12), 84 (40), 83 (10), 82 (17), 69 (14), 68 (14), 67 (14), 55 (33), 43 (12), 42 (43), 41 (42).
1c: $[\alpha]_D$ -137.8 (*c* = 1.2 in CH_2Cl_2); IR (CCl_4) 1690, 1574 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (*t*, 3 H, CH_2CH_3), 1.89-1.97 (*m*, 4 H, ring CH_2), 2.44 (*s*, 3 H, CH_3), 3.28 (*s*, 6 H, CH_3), 3.05-3.45 (*m*, 6 H, CH_2O, CHN), 4.03 (*q*, 2 H, CH_2CH_3), 4.62 (*s*, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 14.46, 16.99, 26.07, 56.79, 58.85, 58.99, 75.78, 88.08, 158.36, 169.28; GC-MS *m/z* 271 (M^+, 2), 226 8100), 114 (12), 82 (12), 71 (45), 45 (17).
20. **3**: from **1b** 33% yield; from **1c** 36 % yield; IR (CCl_4) 3433, 1736, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (*t*, 3 H, CH_2CH_3), 1.28 (*t*, 3 H, CH_2CH_3), 2.35 (*s*, 3 H, CH_3CO), 4.10 (*q*, 2 H, CH_2CH_3), 4.24 (*q*, 2 H, CH_2CH_3), 5.04 (*d*, 1 H, CHN), 5.83-5.85 (*br*, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 14.08, 14.48, 27.88, 61.61, 62.63, 64.42, 155.73, 166.26, 198.67; GC-MS *m/z* 217 (M^+, 1.2), 175 (66), 144 (19), 129 (94), 101 (100), 74 (51), 72 (21), 56 (20), 43 (56).
8: IR (CCl_4) 3403, 1751, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15-1.30 (2*t*, 6 H, OCH_2CH_3), 1.55-2.54 (*m*, 7 H, ring CH_2, CHCO), 2.99-3.12 (*m*, 1 H, CHCO), 4.09 (*q*, 2 H, OCH_2CH_3), 4.19 (*q*, 2 H, OCH_2CH_3), 6.18-6.26 (*br*, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 13.94, 14.45, 22.11, 27.40, 37.74, 39.25, 61.03, 62.10, 68.66, 155.01, 168.05, 202.44; GC-MS *m/z* 257 (M^+, 18), 211 (12), 185 (12), 184 (99), 156 (100), 140 (24), 139 (11), 138 (44), 112 (84), 110 (11), 84 (70), 82 (23), 67 (27), 55 (21), 54 (32), 41 (19).