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The Tandem Michael-SN2 Reaction For The Construction Of The 3-Azabicyclo[3.1.0]hexane Ring System

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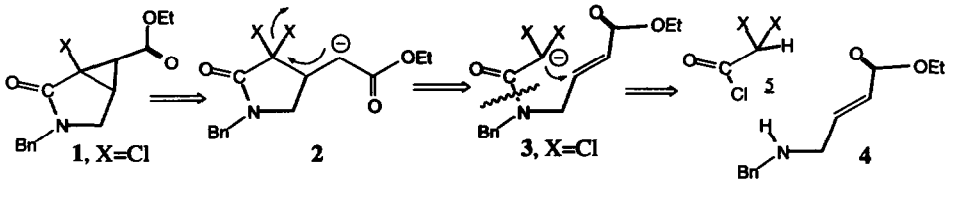
Key Words

Intramolecular Michael; Intramolecular SN2; 3-Azabicyclo[3.1.0]hexane; 3-Azabicyclo[4.1.0]heptane; Dichloroacetic acid.

Abstract: The 3-azabicyclo[3.1.0]-hexane ring system was constructed in a convergent one-pot procedure starting from readily available starting materials, using the intramolecular tandem Michael-SN2 reaction. The methodology was also extended to the synthesis of 3-azabicyclo[4.1.0]heptane ring system.

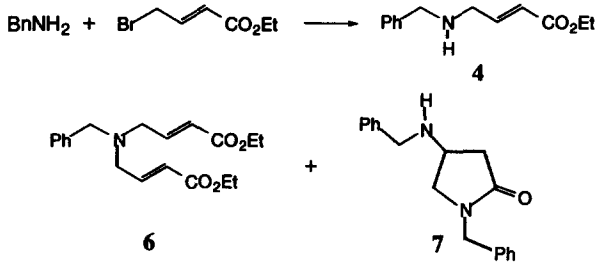
In connection with one of our projects, we required a safe and general method for the construction of a functionalized 3-azabicyclo[3.1.0]hexane ring system. The reaction of ethyl diazoacetate with maleimides[1] is one of the most common methodologies to assemble this ring system. While this is an efficient process, the scale-up of a diazo-containing molecule is not trivial. The formation of 1,2-cyclopropanedicarboxylic acid esters from the reaction of α-haloesters with α,β-unsaturated esters has been described and studied in detail.[2,3]

The extension of this methodology in the intramolecular sense seemed plausible for the construction of the requisite five-three ring system via the tandem Michael-SN2 reaction sequence.[4] Retrosynthetically, the desired product **1** could arise by treating intermediate **3** with base to form **2** which undergoes intramolecular cyclopropanation. Amido ester **3** could be assembled via the amide bond formation of an allyl amine and dichloroacetyl chloride. Compound **3** would then contain both the Michael acceptor (vinyl ester) and a chloride leaving group.

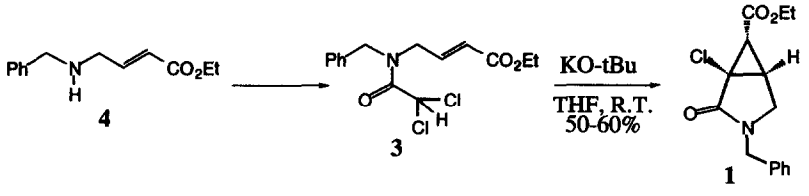


To the best of our knowledge, chloroacetamides cyclizations on activated double bonds are not known. However, cyclizations of chloroacetamides with unactivated double bonds are well established and these proceed in the presence of n-Bu_3SnH[5] or in the presence of CuCl[6,7].

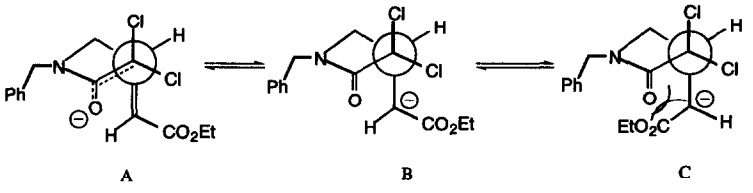
In the forward direction, the reaction of benzylamine with ethyl 4-bromocrotonate provided a readily separable mixture of the desired compound **4** (45%), the diamine **6** (5%), and the pyrrolidine **7** (3%).[8]



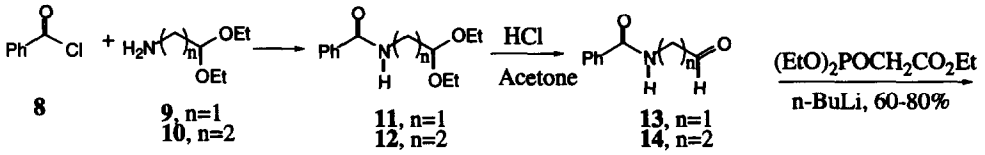
Treatment of **4** with dichloroacetyl chloride in the presence of triethylamine provided amide **3**. Considerable experimentation was required to find the appropriate base to achieve the desired tandem cyclization. In most cases, the base destroyed the starting material **3**, and in some cases only one cyclization (five ring) occurred. Cyclization of **3** was best accomplished with potassium *tert*-butoxide at room temperature in 50-60% isolated yield.



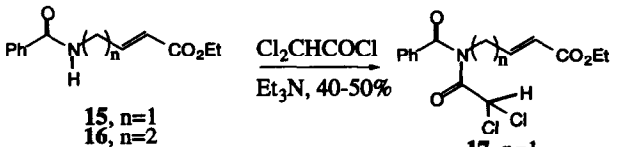
The course of the reaction is noteworthy in that the first cyclization intermediate may be isolated under certain conditions[9]. This would indicate that carbene[10] formation is not occurring and the course of the reaction is strictly a stabilized anion attacking the α,β-unsaturated ester. The stereochemistry of the reaction may be rationalized by the Newman projection depicted below[11] and is consistent with compounds produced via different routes.[1] The reversibility of the Michael reaction allows for the formation of the desirable thermodynamic product **1** probably through the more stable intermediate B.



The use of the allylic amine **4** limits this chemistry to the construction of the 3-azabicyclo[3.1.0]hexane ring system. An extension of this methodology where-by similar chemistry may be utilized to form a 3-azabicyclo[4.1.0]heptane ring system would be desirable. This was achieved by reacting benzoyl chloride with the appropriate amine acetals **9**[12] and **10**. Hydrolysis of the acetals with aqueous hydrochloric acid in the presence of acetone provided the aldehydes **13** and **14** respectively. Olefination of the aldehydes with lithium triethyl phosphonoacetate[13] followed by adding dichloroacetyl chloride in the presence of triethylamine provided the requisite cyclization systems **17** and **18**.

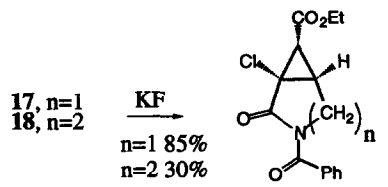


8 **9**, n=1 **10**, n=2 **11**, n=1 **12**, n=2 **13**, n=1 **14**, n=2



15, n=1 **16**, n=2 **17**, n=1 **18**, n=2

As described for compound **3**, the tandem Michael-S_N2 reactions of **17** and **18** were also base dependent and potassium fluoride in acetonitrile at reflux, was the preferred base for the cyclization in both cases. Compounds **19** and **20** were obtained in 85% and 30% isolated yields, respectively. There were no attempts to optimize the reaction of **18** to **20**. The structure and stereochemistry of intermediate **20** were confirmed by X-ray crystallography[14].



17, n=1 **18**, n=2 **19**, n=1 **20**, n=2

In conclusion, we have developed novel methodology for the construction of the 3-azabicyclo[3.1.0]hexane and the 3-azabicyclo[4.1.0]heptane ring systems by utilizing the intramolecular tandem Michael-S_N2 reaction. The multifunctionalities of these intermediates are useful for further manipulations. The choice of base is very critical to the success of the cyclization of each intermediate. This cyclization proceeds via a carbanion addition to an α,β-unsaturated ester which forms a five-membered ring intermediate, that may be isolated. This is then followed by an intramolecular S_N2 closure to form the three-membered ring. This methodology may be extended to form larger ring systems.

Supplementary Material Available: Parameters and coordinates for the X-ray crystallographic analysis of compound **20** (9 pages).

EXPERIMENTAL SECTION

General comments

Melting points were determined with Thomas-Hoover capillary melting point apparatus and were uncorrected. NMR and CMR spectra were recorded on a Brucker 300MHz spectrometer. Microanalyses were performed by the Pfizer Analytical Department. All reagents were used as they were received without any purification. All yields indicate isolated pure products either by chromatography on silica gel or by crystallization where appropriate. $MgSO_4$ was used as a drying agent unless otherwise noted.

Ethyl-(N-benzyl-N-dichloroacetyl)-4-aminobut-2-eneoate (3)

Ethyl-(N-benzyl)-4-aminobut-2-eneoate (2.4 g, 11.0 mmol) (prepared as in reference 8) was dissolved in 35 ml of CH_2Cl_2, cooled to 0°C with an ice bath, and dichloroacetyl chloride (1.60 ml, 16.5 mmol) was added. Triethylamine (2.3 ml, 16.5 mmol) in 10 ml of CH_2Cl_2 was then added dropwise over a period of 30 min. The reaction was allowed to stir at 0°C for 30 min and at 25°C for 30 additional min. The reaction was judged complete by TLC (20% ethyl acetate-80% hexane) and it was partitioned between 50 ml of CH_2Cl_2 and 20 ml of water. The organic layer was washed with 20 ml of 1N aqeous HCl solution and was dried. The residual oil was purified by chromatography using 100 g of coarse silica (63-200 mesh) and 20% ethyl acetate/80% hexane solvent system to isolate 1.63 g of the product as a brown oil (45% yield). NMR(rotomers): 7.4-7.2 (m, 5H, aromatic), 6.91-6.75 (m, 1H, vinyl), 6.26 and 6.20 (two singlets, 1H, dichloroacetamide), 5.97-5.82 (m, 1H, vinyl), 4.74 and 4,61 (two singlets, 1H, benzyl), 4.27-4.1 (m, 4H, CH_2 of the ethyl group, and CH_2 allylic), 1.3 (q, CH_3). CMR($CDCl_3$, rotomers) 165.7, 165.3, 164.2, 164.1 (vinyl H's), 141.2, 140.7, 135.4, 134.6, 129.2, 128.9, 128.4, 128.1, 126.7, 123.9, 123.3 (aromatics), 65.1 and 64.9 (d), 60.9 and 60.7 (t), 51.3 and 49.5 (t), 47.5 and 47.0 (t), 14.2 (q). Exact mass calcd for $C_{15}H_{17}NO_3Cl_2$ 329.0581, found M+1 330.0639. Anal. calcd for $C_{15}H_{17}NO_3Cl_2$: C, 54.56; H, 5.19; N, 4.24; Cl, 21.47. Found: C, 54.50; H, 5.10; N, 4.05; Cl, 21.55.

1-Chloro-2-oxo-3-benzyl-6-carboethoxy-3-azabicyclo[3.1.0] hexane (1)

Ethyl-(N-benzyl-N-dichloroacetyl)-4-aminobut-2-eneoate **3** (1.02 g, 3.1 mmol) was dissolved in 20 ml of THF. To that was added potassium t-butoxide (6.35 ml, 12.4 mmol, 1.95 M solution in THF) at 25°C. The reaction turned brown immediately and there was no starting material left by TLC analysis (40% ethyl acetate, 60% hexane). The reaction was diluted with 80 ml of CH_2Cl_2 and washed with 20 ml of water, 20 ml of saturated aqueous sodium bicarbonate solution, 30 ml of brine, and dried. Removal of the solvent provided an oil which was chromatographed on 20 g of fine silica gel (230-400 mesh) using 30% ethyl acetate in hexane. This provided 546 mg of the desired product (60% yield). NMR($CDCl_3$): 7.34-7.11 (m, 5H, aromatic), 4.45 (d, 1H, J= 14.6 Hz, benzyl), 4.27 (d, 1H, 14.55 Hz, benzyl), 4.10 (q, 2H, CH_2 ethyl, J= 7.1 Hz), 3.45 (dd, 1H, J= 5.24, 11.2 Hz), 3.04 (d, 1H, J= 11.3 Hz), 2.85 (dd, 1H, J= 3.8, 1.28 Hz), 1.69 (d, 1H, J= 3.7 Hz), 1.28 (t, 3H, methyl, J= 7.1 Hz). CMR($CDCl_3$): 171.7 (s), 167.1 (s), 136.2 (s), 128.8 (d), 128.2 (d), 127.8 (d), 78.8 (s), 61.03 (t), 46.71 (t), 45.82 (t), 31.18 (d), 14.22 (q). Exact mass calcd for $C_{15}H_{16}NO_3Cl$

293.0819, found: 293.0857. Anal. calcd for $C_{15}H_{16}NO_3Cl$: C, 61.33; H, 5.49; N, 4.77; Cl, 12.07. Found: C, 61.20; H, 5.48; N, 4.66; Cl, 12.02.

3,3-Diethoxy-N-benzoylpropylamine (12)

To 3,3-diethoxypropylamine (1.2 g, 8.15 mmol) in 25 ml of CH_2Cl_2 was added triethylamine (1.10 ml, 8.15 mmol) and the mixture was cooled to 0°C. Benzoyl chloride (1.15 g, 8.15 mmol) was added as a solution in 5 ml of CH_2Cl_2. Solids started forming immediately and the reaction was allowed to stir at 25°C for 16 h. The reaction was partitioned between 50 ml of CH_2Cl_2 and 15 ml of 10% aq. HCl solution. The organic layer was washed with an additional 15 ml of 10% aq. HCl solution, 25 ml of brine and dried. Evaporation of the solvent provided 1.67 g of a yellow oil which was used as is without purification. NMR($CDCl_3$): 7.78 (m, 2H, aromatic), 7.39-7.5 (m, 3H, aromatic), 7.05 (broad, 1H, amide proton), 4.65 (t, 1H, a-diethoxy, J=5 Hz), 3.78-3.5 (m, 6H, alpha to amide and CH_2 of ethyl), 1.96 (m, 2H), 1.23 (t, 6H, methyls, J=7.04 Hz). CMR($CDCl_3$): 134.8 (s), 131.2 (d), 128.5 (d), 126.8 (d), 103.1 (d), 62.2 (t), 35.96 (t), 32.7 (t), 15.4 (q). Exact mass calcd for $C_{14}H_{21}NO_3$: 251.1521, found M-OEt: 206.1172.

N-Benzoyl-1-amino-3-propanal (14)

3,3-diethoxy-N-benzoylpropylamine **12** (1.1 g, 4.38 mmol), was dissolved in 20 ml of acetone and 25 ml of 10% aq. HCl solution was added. The mixture was allowed to stir at 25°C for 16 h. The acetone was removed under reduced pressure and the aqueous layer was extracted 3X50 ml fractions of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to obtain 610 mg of a white solid which required no purification. NMR($CDCl_3$): 9.78 (s, 1H, aldehyde), 7.74-7.3 (m, 5H, aromatic), 6.96 (broad, 1H, amide H), 3.70 (dd, 2H, 5.8 Hz), 2.79 (dd, 2H, 5.6 Hz). CMR($CDCl_3$): 167.6 (s), 134.2 (s), 131.6 (d), 128.5 (d), 126.9 (d), 43.69 (t), 33.49 (t). Exact mass calcd for $C_{10}H_{11}NO_2$: 177.0790, found: 177.0798. Mp: 73-74°C.

Ethyl-[(N-benzoyl)-5-amino]pent-2-eneoate (16)

A solution of triethyl phosphonoacetate (569.0 mg, 2.54 mmol) in 10 ml of THF was cooled to -78°C and n-BuLi (1.2 ml, 2.54 mmol, 2.5 M solution in hexane) was added. After 30 min. the aldehyde (450 mg, 2.54 mmol) was added dropwise as a solution in 5 ml of THF. The reaction was allowed to stir at -78°C for 1h, and was allowed to warm to room temperature over a period of 1h. The reaction was quenched with 10 ml of water and the mixture was extracted with 2 X 60 ml of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to obtain a yellow oil. GC analysis of this oil showed a 10:1 ratio of trans to cis isomers. The desired trans isomer (220 mg) was isolated by chromatography on silica gel (230-400 mesh) (30:1 silica to compound) using 25% ethyl acetate-75% hexane. No attempts at improving the yield or ratio were undertaken. NMR for the cis isomer: 7.75 (m, 2H, aromatic), 7.48 (m, 3H, aromatic), 6.29 (m, 1h, vinyl), 5.88 (m, 1H, vinyl), 4.15 (q, 2H, ethyl CH_2), 3.56 (m, 2H), 2.88 (m, 2H), 1.24 (t, 3H, methyl). Analytical for trans compound: NMR: 7.75-7.28 (m, 5H, aromatic), 7.16 (m, 1H, amide), 6.92-6.71 (triplet of doublets, 1H, vinyl, J=15, 7 Hz), 5.81 (m, 1H, vinyl, J=15.7, 1.5 Hz), 4.1 (q, 2H ethyl) 3.50 (dd, 2H, J=6.8, 12.8 Hz), 2.45(m, 2H), 1.20 (t, 3H, methyl). CMR: 167.9 (s), 166.3 (s), 145.5 (d), 134.4 (s), 131.4 (d), 128.4 (d), 126.8 (d), 123.2 (d), 60.29 (t), 38.47 (t), 32.16 (t), 14.18 (q). Exact mass calcd for $C_{14}H_{17}NO_3$: 247.1208, found: 247.1187. Mp: 74-76°C.

Ethyl-[(N-benzoyl-N-dichloroacetate)-5-amino]pent-2-eneoate (18)

Ethyl-[(N-benzoyl)-5-amino]pent-2-eneoate **16** (2.27 g, 9.2 mmol) and dichloroacetyl chloride (1.3 ml, 13.8 mmol) were mixed in 50 ml of 1,2-dichloroethane and heated to reflux. Triethylamine (1.3 ml, 9.2 mmol) was added slowly via syringe pump over a period of 5 h. The reaction was judged complete by TLC (25% ethyl acetate in hexane) and was cooled to room temperature. 50 ml of 1,2-dichloroethane was added and the mixture was washed with 20 ml of 10% aq. HCl solution, 30 ml of brine and dried. Evaporation of the solvents provided a solid which crystallized from hot diisopropyl ether. We obtained 2.31 g of product as first crop (70% yield). A second crop was obtained but the purity was not as good (520 mg) and this material was not used in the next step. NMR($CDCl_3$): 7.67-7.49 (m, 5H, aromatic), 6.74 (m, 1H, vinyl), 6.69 (s, 1H, dichloroacetyl), 5.80 (dd, 1H, vinyl, J=15.7, 1.45 Hz), 4.15 (q, 2H, ethyl J=7.2 Hz), 3.90 (t, 2H, J=7.1 Hz), 2.5 (m, 2H), 1.29 (t, 3H, methyl J=7.2 Hz). CMR($CDCl_3$): 173.6 (s), 167.3 (s), 165.8 (s), 143.1 (d), 133.5 (d), 133.3 (s), 129.3 (d), 128.7 (d), 124.5 (d), 66.19 (d), 60.42 (t), 46.82 (t), 31.07 (t), 14.22 (q). Exact mass calc. for $C_{16}H_{17}NO_4Cl_2$ 357.0535, found 357.0509. Anal. calcd for $C_{16}H_{17}NO_4Cl_2$: C, 53.65; H, 4.78; N, 43.91; Cl, 19.79. Found: C, 53.69; H, 4.72; N, 3.92; Cl, 19.78. Mp: 74-76°C.

1-Chloro-2-oxy-3-benzoyl-7-carboethoxy-3-azabicyclo[4.1.0] heptane (20)

Ethyl-[(N-benzoyl-N-dichloroacetate)-5-amino]pent-2-eneoate **18** (720 mg, 2.02 mmol) was dissolved in 10 ml of acetonitrile and potassium fluoride (210 mg, 3.61 mmol) was added. The reaction was heated to reflux for 3 h and TLC analysis showed some starting material was still left (Rf of product = 0.2 and Rf of starting material = 0.32 in 25% ethyl acetate-75% hexane). An additional 430 mg of potassium fluoride (7.4 mmol) was added and heating was continued for 6 h. The reaction was concentrated down to an oil which was partitioned between 20 ml of water and 80 ml of CH_2Cl_2. The organic layer was washed with 10 ml of saturated aq. $NaHCO_3$ solution, dried, and evaporated. The residual oil was chromatographed on silica gel using 20% ethyl acetate in hexane and 195 mg of desired product was isolated (30% yield). NMR($CDCl_3$): 7.6-7.4 (m, 5H, aromatic), 4.29, 2H, ethyl, J=7.1 Hz), 4.20 (m, 1H), 3.40 (ddd, 1H, J=1.8, 4.9 Hz), 2.85 (m, 2H), 2.45-2.32 (m, 1H), 2.29-2.2 (m, 1H), 2.37 (t, 3H methyl, J=7Hz). CMR($CDCl_3$): 173.5 (s), 167.0 (s), 166.1 (s), 135.1 (s), 132.0 (d), 128.4 (d), 127.9 (d), 62.19 (t), 45.51 (s), 41.61 (t), 30.65 (d), 30.45 (d), 19.74 (t), 14.24 (q). Exact mass calcd for $C_{16}H_{16}NO_4Cl$: 321.0768, found: 321.0764. Anal. calcd for $C_{16}H_{16}NO_4Cl$: C, 59.73; H, 5.01; N, 4.35; Cl, 11.02. Found: C, 59.83; H, 4.92; N, 4.32; Cl, 11.28. Mp: 140-141°C.

Ethyl-[(N-Benzoyl)-4-amino]but-2-eneoate (15)

Triethyl phosphonoacetate (1.24 g, 5.53 mmol) in 10 ml of THF was cooled to -78°C and n-BuLi (2.21 ml, 5.53 mmol, 2.5 M solution in hexane) was added. After 30 min the aldehyde **13** (1000 mg, 6.14 mmol) was added dropwise as a solution in 15 ml of THF. The reaction was allowed to stir at -78°C for 1h, and was allowed to warm to 25°C over a period of 1h. 10 ml of water was added to the reaction and the mixture was extracted with 2 X 100 ml of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated to obtain a yellow oil. GC analysis of this oil showed an 8:1 ratio of trans to cis isomers. The desired trans isomer (1.1 g, 70%) was isolated by chromatography on fine silica gel (25:1 silica to compound) using 25% ethyl acetate/75% hexane. No attempts at improving the yield or ratio were undertaken. NMR($CDCl_3$) for the

cis compound: 7.78 (m, 2H, aromatic), 7.61 (m, 1H, amide H), 7.45-7.29 (m, 3H, aromatic), 6.26 (m, 1H, vinyl), 5.78 (m, 1H, vinyl), 4.48 (m, 2H), 4.10 (q, 2H, CH_2 ethyl), 1.21 (t, 3H, methyl). Analytical data for the trans compound: NMR($CDCl_3$): 7.80-7.35 (m, 5H, aromatic), 6.96 (m, 1H, amide), 6.92 (m, 1H, vinyl), 5.93 (m, 1H, vinyl), 4.2-4.11 (m, 4H, two CH_2), 1.27 (t, 3H, methyl). CMR($CDCl_3$): 167.6 (s), 166.1 (s), 144.0 (d), 133.9 (s), 131.8 (d), 128.6 (d), 127.1 (d), 121.8 (d), 60.53 (t), 40.60 (t), 14.21 (q). Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.56; H, 6.65; N, 5.84. Exact mass calcd for $C_{13}H_{15}NO_3$: 233.1052, found: 233.1024.

Ethyl-[(N-benzoyl-N-dichloroacetate)-4-amino]but-2-eneoate (17)

Ethyl-[(N-benzoyl)-4-amino]but-2-eneoate **15** (1.33 g, 5.70 mmol), and dichloroacetyl chloride (1.1 ml, 11.4 mmol) were mixed in 50 ml of CH_2Cl_2 and heated to reflux while triethylamine (1.60 ml, 11.4 mmol) was added slowly via syringe pump over a period of 2 h. The reaction was allowed to stir for 2 additional hours and was judged complete by TLC (25% ethyl acetate in hexane). The reaction was cooled to room temperature and 50 ml of CH_2Cl_2 was added. The mixture was washed with 20 ml of 10% aq. HCl solution, 30 ml of brine and dried. Evaporation of the solvents provided a brown oil which was chromatographed on coarse silica using 20% ethyl acetate in hexane, to give a solid which was recrystallized from hot diisopropyl ether. Obtained 700 mg of clean product (36% yield). A second crop of solids was isolated after 24 h. This batch weighed 368 mg. Total yield for the reaction 55%. NMR($CDCl_3$): 7.67-7.47 (m, 5H, aromatic), 6.90 (m, 1H, amide), 6.88 (s, 1H, dichloroacetyl), 6.79 (m, 1H, vinyl), 5.88 (dd, 1H, vinyl J=15.8, 1.74 Hz), 4.50 (dd, 2H, J=1.71, 5.2 Hz), 4.20 (t, 2H, CH_2, J=7.2 Hz), 1.28 (t, 3H, J=7.1 Hz). CMR($CDCl_3$): 173.4 (s), 167.0 (s), 165.4 (s), 140.3 (d), 133.6 (d), 132.8 (s), 129.2 (d),128.5 (d), 123.8 (d), 66.24 (d), 60.79 (t), 48.43 (t), 14.19 (q). Anal. calcd for $C_{15}H_{15}NO_4Cl_2$: C, 52.34; H, 4.39; N, 4.07; Cl, 20.60. Found: C, 52.52; H, 4.20; N, 4.05; Cl, 20.62. Mp: 82-83°C.

1-Chloro-2-oxo-3-benzoyl-6-carboethoxy-3-azabicyclo[3.1.0]hexane (19)

Ethyl-[(N-benzoyl-N-dichloroacetate)-4-amino]but-2-eneoate **17** (220.3 mg, 0.64 mmol), was dissolved in 10 ml of acetonitrile and potassium fluoride (161 mg, 2.73 mmol) was added. The mixture was heated to reflux for 4 h. The solvent was removed under reduced pressure and the residue was partitioned between 55 ml of CH_2Cl_2 and 10 ml of water. The organic layer was dried, evaporated and chromatographed on 5.5 g of fine silica using 20% ethyl acetate in hexane. The desired product was isolated in 85% yield (166 mg). NMR($CDCl_3$): 7.6-7.38 (m, 5H, aromatic), 4.28 (2H, ethyl CH_2), 4.20 (m, 1H), 3.86 (d, 1H, J=12.2 Hz), 3.03 (t, 1H, J=4.61 Hz), 1.32 (t, 3H, methyl). CMR($CDCl_3$): 169.6 (s), 168.0 (s), 165.6 (s), 133.2 (s), 129.0 (d), 128.6 (d), 128.1 (d), 62.23 (t), 48.5 (s), 45.87 (t), 32.26 (d), 25.98 (d), 14.24 (q). Anal. calcd for $C_{15}H_{14}NO_4Cl$: C, 58.55; H, 4.59; N, 4.55. Found: C, 57.96; H, 4.57; N, 4.65. Exact mass calcd for $C_{15}H_{14}NO_4Cl$: 307.0608. Found: 308.0690 (M+1). Anal. calcd for $C_{15}H_{14}NO_4Cl$: C, 58.55; H, 4.59; N, 4.55; Cl, 11.52. Found: C, 57.96; H, 4.57; N, 4.65; Cl, 11.50.

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