ORGANIC LETTERS

2006
Vol. 8, No. 8
1717−1719

Novel Bicyclization Reaction Leading to a Fused β-Lactone

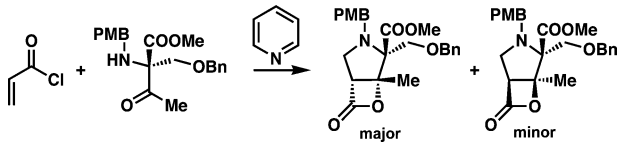
Leleti Rajender Reddy and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

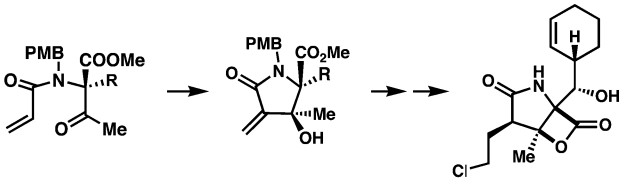
Received February 22, 2006

ABSTRACT



The reaction of acrylyl chloride with the above amino ketone in the presence of pyridine produces bicyclic β-lactones rather than the corresponding acrylamide, which can be the major product under other conditions.

We recently developed two different stereocontrolled syntheses of the potent antitumor agent and proteasome inhibitor salinosporamide A (**1**) which involved two methods for the cyclization of keto amide **2** to γ-lactam **3** (**a** or **b** series).[1,2] The synthesis of the acrylamide **2** (**a** or **b** series) was carried out by the coupling of acrylyl chloride with the *N*-*p*-methoxybenzyl-substituted amino ketone **4** (**a** or **b** series).



2a, R = CH_2OCH_2Ph
2b, R = CH(OTBS)*i*-Pr

3a, R = CH_2OCH_2Ph
3b, R = CH(OTBS)*i*-Pr

1

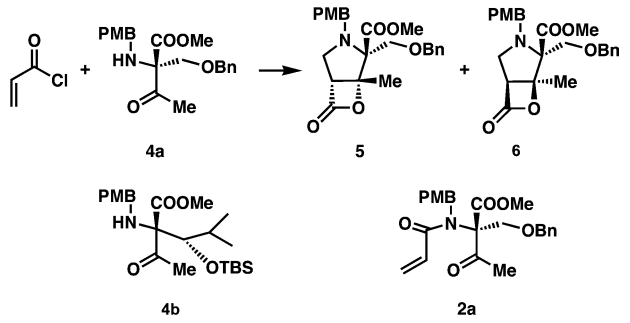
The efficient conversion of **4** to **2** required considerable experimentation, and it represents an interesting example of how amide formation, one of the most straightforward, reliable, and general reactions in organic chemistry, can be anything but simple, especially for **2b** (R = CH(OTBS)*i*-Pr). The process eventually adopted for the transformation, e.g., for **4a** → **2a**, involved the portionwise addition to **4a** of 9 equiv of acrylyl chloride and 9 equiv of triisobutylamine in acetonitrile as solvent at 23 °C over 4 days, which afforded the product **2a** in 79% yield. The problem in this coupling arises from the combination of low basicity and high steric screening of the amino group of **4a** or **4b** which results in a reaction rate that is so slow that much self-condensation of acrylyl chloride occurs. Another, and more interesting, problem is the occurrence of a novel side reaction which can become dominant under certain reaction conditions. In this paper, we present a study of that unusual reaction, the conditions that favor it at the expense of acrylamide formation, and also a possible reaction pathway.

The optimum bases for formation of acrylamide were highly hindered tertiary amine-type reagents such as, for example, triisobutylamine or 2,6-di-*tert*-butylpyridine. The yield of acrylamide **2a** using 2,6-di-*tert*-butylpyridine (82%) is actually slightly higher than that for triisobutylamine (79%), and the ratio of acrylamide **2a** to the byproduct is considerably higher: greater than 40:1 for 2,6-di-*tert*-butylpyridine vs 14:1 for triisobutylamine. The byproducts from **4a** were established unambiguously to be the β-lactone **5** and the diastereomer **6** from NMR, IR, and mass spectral data and single-crystal X-ray diffraction analysis of **5**. Pure **5**, obtained by crystallization of the mixture of **5** and **6** (generally 4:1), is a colorless crystalline solid (mp 118−

(1) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230−6231.

(2) Reddy, L. R.; Fournier, J. F.; Subba Reddy, B. V.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8974−8976.

10.1021/ol060464n CCC: $33.50
Published on Web 03/24/2006



120 °C, $[\alpha]^{23}_D$ −48.9 (c = 0.65, $CHCl_3$)) that exhibits a carbonyl stretching band at 1826 cm^{-1} but no amide carbonyl band (COOMe at 1722 cm^{-1}). Physical characterization data and procedures for the synthesis of **5**[3] and acrylamide **2a**[4] appear below. The optimum base for formation of β-lactone was found to be pyridine which resulted in a yield of **5** of 80% and a ratio of β-lactone to acrylamide of 8:1. An ORTEP diagram for the bicyclic β-lactone **5** is displayed in Figure 1.

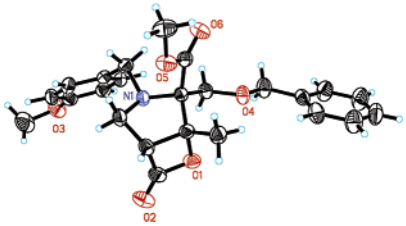
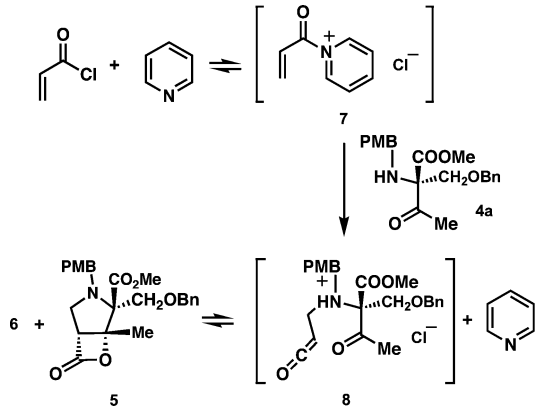


Figure 1. ORTEP diagram for **5**.

The observation that the course of the reaction of acrylyl chloride with the amino ketone **4a** (or **4b**) depends critically on the nature of the amine coreactant has important mechanistic implications. The ratio of acrylamide **2a** to β-lactones (**5** + **6**) has been found to vary with the catalytic amine as follows: for 2,6-lutidine, 2.2:1; for pyridine, 8:1; for Et_3N, 2.5:1; for 2,6-di-*tert*-butylpyridine, >1:40; for triisobutylamine, 1:14, all under the standard conditions.[3,4] We believe that the mechanistic pathway for pyridine as base that favors β-lactone formation is most likely to be the following:



If that is the case, it follows that the likely pathway from **4a** to the acrylamide **2a** involves N-acylation of **4a** by acrylyl chloride itself, the function of the amine being simply to serve as a stoichiometric proton acceptor. This interpretation provides a logical explanation for the fact that the most hindered bases, 2,6-di-*tert*-butylpyridine and triisobutylamine, do not lead to β-lactone, but instead to acrylamide **2a**. These highly hindered bases would not be expected to provide activated *N*-acrylylammonium complexes analogous to the pyridinium complex **7**. Nucleophilic attack by the secondary amine on the activated electrophile **7**, which could in principle occur either at the CO group or at the carbon β to CO, probably occurs preferentially at the latter for steric reasons (the amino group in **4a** is encumbered by the attached substituents). Sterically preferred Michael addition of the amine **4a** to **7** leads to a keto ketene (**8**) which then cyclizes by internal [2+2]-cycloaddition to give the β-lactones **5** and **6**. This internal cycloaddition process, which could be very useful in synthesis, is precedented by a small number of examples in the literature.[5]

(3) **(4*R*,5*R*,6*R*)-4-Benzyloxymethyl-3-(4-methoxybenzyl)-5-methyl-7-oxo-6-oxa-3-aza-bicyclo[3.2.0]heptane-4-carboxylic Acid Methyl Ester, 5:** To a solution of amino ketone **4a** (1.85 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was added pyridine (1.22 mL, 15.0 mmol) at 0 °C and then acrylyl chloride (0.80 mL, 10 mmol) (added dropwise with stirring at 0 °C). The reaction mixture was stirred for 12 h at 23 °C, and the solvent was removed in vacuo to afford the crude product. This mixture was purified by column chromatography (silica gel, ethyl acetate−hexane, 1:10 then 1:4) to give bicyclic β-lactone **5**, the diastereomer **6** (1.70 g, 80%), and the acrylamide **2a** (0.20 g, 10%). Crystallization of the mixture of lactones from ether−hexane provided colorless crystals of **5**. Found for **5**: R_f = 0.81 (50% ethyl acetate in hexanes); mp = 118−120 °C; $[\alpha]^{23}_D$ = −48.9 (c 0.65, $CHCl_3$); FTIR (film) ν_{max} 3050, 2990, 1826, 1722, 1511, 1241, 1102, 1032, 825, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (5H, m), 7.12 (2H, d, J = 8.8 Hz), 6.81 (2H, d, J = 8.8 Hz), 4.55 (2H, dd, J = 21.6, 12.0 Hz), 4.02 (1H, d, J = 9.2 Hz), 3.92 (1H, d, J = 13.6 Hz), 3.87 (1H, d, J = 8.8 Hz), 3.81 (3H, s), 3.78 (3H, s), 3.52 (1H, d, J = 6.4 Hz), 3.19 (1H, d, J = 10.0 Hz), 3.16 (1H, d, J = 13.6 Hz), 2.82 (1H, dd, J = 10.0, 6.4 Hz), 1.83 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.09, 169.62, 159.07, 138.25, 130.31, 129.43, 129.17, 128.82, 128.52, 128.00, 127.77, 127.69, 114.09, 88.15, 74.13, 73.40, 70.82, 58.47, 55.50, 53.54, 51.70, 50.67, 19.80; HRMS (ESI) calcd for $C_{24}H_{28}NO_6$ (M + H)$^+$ 426.1916, found 426.1918.

(4) **(*R*)-Methyl-2-(benzyloxymethyl)-2-[*N*-(4-methoxybenzyl)acrylamido)]-3-oxobutanoate, 2a:** To a solution of the amino ketone **4a** (1.85 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was added 2,6-di-*tert*-butylpyridine (2.81 g, 15.0 mmol) at 0 °C and then acrylyl chloride (0.80 mL, 10 mmol) (dropwise with stirring at 0 °C). After 12 h at 23 °C (reaction complete by TLC analysis), the reaction mixture was diluted with ethyl acetate (25 mL) and washed with 2 N HCl and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude product. This mixture was purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:10 then 1:4) to afford pure amide **2a** as a colorless solid (1.74 g, 82%). Found: R_f = 0.80 (50% ethyl acetate in hexane); mp = 85−86 °C; $[\alpha]^{23}_D$ −12.75 (c 1.45, $CHCl_3$); FTIR (film) ν_{max} 3030, 2995, 1733, 1717, 1510, 1256, 1178, 1088, 1027, 733, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (2H, d, J = 8.0 Hz), 7.25 (3H, m), 7.11 (2H, m), 6.88 (2H, d, J = 9.0 Hz), 6.38 (2H, m), 5.63 (1H, dd, J = 8.5, 3.5 Hz), 4.93 (1H, d, J = 18.5 Hz), 4.78 (1H, d, J = 18.5 Hz), 4.27 (2H, m), 3.78 (3H, s), 3.76 (3H, s), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.12, 169.23, 168.62, 158.01, 136.95, 130.64, 130.38, 128.63, 128.13, 127.77, 127.32, 114.33, 77.49, 73.97, 70.66, 55.49, 53.09, 49.03, 28.24; LRMS (m/z, %) 426 (M$^+$ + 1) (100); HRMS (ESI-MS) calcd for $C_{24}H_{28}NO_6$ 426.1916, found 426.1909 (M + H)$^+$. Because triisobutylamine is much less expensive than 2,6-di-*tert*-butylpyridine and the yield of **2a** is only slightly less (78%), it is the preferred reagent for larger-scale preparations.

The pyridine-promoted pathway to β-lactone is expected to be somewhat faster than the formation of the amide **2a** if the role of 2,6-di-*tert*-butylpyridine or triisobutylamine is simply to serve as a stoichiometric acceptor of HCl. In accord with this expectation was our finding that the reaction of acrylyl chloride with the amine **4a** and a 1:1 mixture of pyridine and triisobutylamine produces β-lactones **5** and **6** predominately and the acrylamide **2a** as a minor product.

(5) (a) Brady, W. T.; Gu, Y. Q. *J. Org. Chem.* **1988**, *53*, 1353−1356. (b) Kabir, S. H.; Seikaly, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 1059−1060. (c) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945−7946. (d) Cortez, G. S.; Oh, S. H.; Romo, D. *Synthesis* **2001**, 1731−1736.

Supporting Information Available: Complete data for the X-ray crystal structure determination for β-lactone **5**. Characterization data for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060464N