ORGANIC LETTERS

2003
Vol. 5, No. 7
1019−1021

One-Pot Synthesis of Polyfunctionalized Cyclic Urea Derivatives

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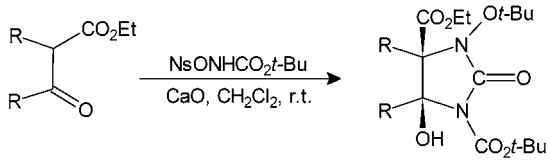
Received December 19, 2002

ABSTRACT



Unexpectedly, imidazolidin-2-ones are easily obtained from *β*-keto esters upon treatment with *tert*-butyl nosyloxycarbamate and calcium oxide under mild conditions. The structure of the product was established by X-ray crystallography.

Some studies on the synthesis of substituted imidazolidin-2-ones or cyclic urea derivatives,[1] which have potential biological activities, have been reported, often as patents. Arylsulfonylbenzimidazolones possess antidiabetic properties.[2] Phosphonate derivatives were used as insecticides, acaricides, and nematocides.[3] Pyridyl-substituted compounds are active against Enterovirus 71.[4] Cyclic ureas are also inhibitors of HIV protease.[5] Ureido-balhimycin is known as a natural antibiotic.[6] Imidazolidin-2-ones can be obtained by ring contraction of uracils, using salts of Tl^{III}.[7]

Recently, we found that *β*-keto esters are aminated by ethyl nosyloxycarbamate ($NsONHCO_2Et$, Ns = 4-nitrophenylsulfonyl, **1a**)[8] at room temperature in the presence of calcium oxide.[9] Hanessian reported that similar sulfonyloxycarbamates, when treated with NaH at low temperatures, gave a surprising alkoxyaminocarbonylation of *β*-dicarbonyl compounds.[10]

In this paper, we report an unexpected reaction of *β*-keto esters and *tert*-butyl nosyloxycarbamate ($NsONHCO_2t$-Bu, **1b**)[11] giving directly imidazolidin-2-ones (Scheme 1).

Ethyl 2-oxocyclohexanecarboxylate (**2**) was treated with **1b** and CaO in the molar ratio substrate:CaO:**1b** = 1:6:2.5 in CH_2Cl_2 at room temperature over 4 h. The reaction mixture was filtered, and the residue was purified by flash chromatography to give **3** (mp 128−129 °C from pentane/chloroform) in 78% yield.

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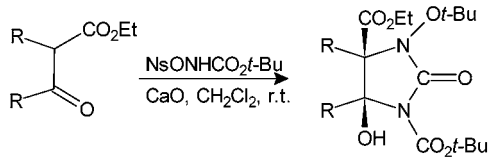
(11) Compound **1b** was obtained according to Lwowski's procedure[8] in 78% yield. Physical and spectroscopic data are in agreement with those reported: Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Hodgson, P. K. G.; Langridge-Smith, P. R. R.; Millar, J. R. A.; Taylor, A. T. *J. Chem. Soc., Chem. Commun.* **1995**, 885−886.

10.1021/ol027509e CCC: $25.00 © 2003 American Chemical Society
Published on Web 03/05/2003

Scheme 1



2 R---R = $-(CH_2)_4-$ **3**

4 R---R = $-(CH_2)_3-$ **5**

6 R = CH_3 **7**

The infrared spectrum showed a broad band centered at 3475 cm^{-1} and three carbonyl absorptions at 1793, 1750, and 1693 cm^{-1}. The electrospray ionization mass spectrum (ESI-MS) showed MH^+ ion at *m*/*z* 401. Elemental analysis gave results consistent with the formula $C_{19}H_{32}N_2O_7$. Its ^1H NMR showed a triplet at δ 1.20 ppm, two sharp singlets at 1.26 and 1.52 ppm, multiplets between 1.56 and 2.59 ppm, the AB part of an ABX system centered at 4.20 ppm, and a singlet at 4.58 ppm (disappeared after treatment with D_2O). The ^{13}C NMR indicated the presence of a methyl at δ 14.0 ppm, three methylenes at 20.2, 20.6, and 24.8 ppm, two sharp methyls at 27.9 and 28.1 ppm, two methylenes at 37.1 and 61.7 ppm, four quaternary carbons at 71.4, 81.9, 84.1, and 85.1 ppm, and three carbonyls at 151.1, 156.9, and 169.0 ppm. However, these physical data did not provide a clear structure for compound **3**. So its structure was determined by X-ray crystallographic analysis, which established **3** to be 7-*tert*-butyl 1-ethyl (1*R**,6*R**)-9-*tert*-butoxy-6-hydroxy-8-oxo-7,9-diazabicyclo[4.3.0]nonane-1,7-dicarboxylate. Figure 1 shows a perspective view of **3**.

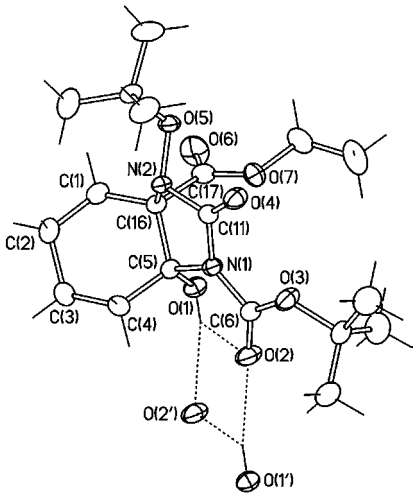
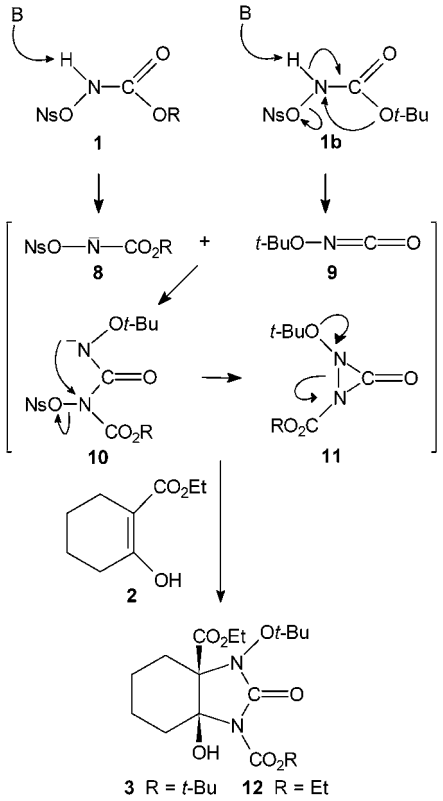


Figure 1. View of the molecular structure of **3**. Ellipsoids are at 30% probability.

The cyclohexyl ring is chair conformed and shares the C(5)−C(16) edge with the imidazolidinone moiety. A closely similar conformation was found in the imidazolidin-2-one ring of ureido-balhimycin.[6] The molecules in the crystal are disposed in pairs related by an inversion center, with the OH group of each molecule facing the O(2) atom of the other. The existence of both a short O(1)···O(2) intramolecular distance, 2.774(2) Å, and a relatively short O(1)···O(2′) intermolecular one, 2.970(2) Å, suggests the presence of bifid hydrogen interactions. The calculations were done by means of the SHELX97 program[12] contained in the WINGX suite.[13]

A possible pathway to explain the unprecedented formation of **3** is depicted in Scheme 2.

Scheme 2



The anion **8** can be obtained from **1**. Base-induced deprotonation with concomitant migration of the *tert*-butoxy group and departure of the arylsulfonyloxy moiety generates *tert*-butoxy isocyanate (**9**), as proposed before.[10] Then, a process involving **8**, **9**, their addition product **10**, the diaziridinone **11** or its "ring-chain" isomer,[14] and the enol form of **2** leads to the final product **3**.

To support the suggested sequence, a crossover experiment was done treating **2** with CaO and an equimolar amount of **1a** and **1b** [molar ratio **2**:CaO:**1a**:**1b** = 1:6:1.5:1.5], since **1a** is known to give the anion **8**,[8,15] while **1b** generates the

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isocyanate intermediate **9**.[10] The major product of the reaction was indeed the imidazolidin-2-one **12**, together with **3** and other expected products.[9] We emphasize that reactions using **1a** alone did not give any product of type **3**.

Other β-keto esters **4** and **6**, in the same conditions, gave analogously the imidazolidin-2-ones **5** and **7** in 58 and 62% yields, respectively.

Thus, a cycloaddition occurs and a 2:1 adduct between the reagent and the substrate is obtained with the concomitant formation of two new carbon−nitrogen bonds. It is noteworthy that only a single regioisomer is always found.

In conclusion, polyfunctionalized imidazolidin-2-ones (cyclic urea derivatives) can be obtained in a one-step, simple, and efficient procedure from commercially available β-keto esters and $NsONHCO_2tBu$, a cheap reagent easy to prepare and store. The results presented here should also approach the requirements of "click chemistry".[16] Normally the synthesis of such compounds requires multistep sequences.

Acknowledgment. We thank the Italian Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) and the Università degli Studi di Roma La Sapienza (National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni") and the Project "Nuove Strategie per il Controllo delle Reazioni: Interazione di frammenti Molecolari con Siti Metallici in Specie non Convenzionali" for financial support.

Supporting Information Available: General procedures, X-ray data of **3**, and details of the spectroscopic characterization of new compounds (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org. X-ray data for compound **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 147868. Copies of the data may be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax, (+44) 1223-336-033; e-mail, deposit@ccdc.cam.ac.uk).

OL027509E

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