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속 보

3-Oxa-2,7-diazabicyclo[3.3.0]oct-1-ene의 합성

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Facile Synthesis of 3-Oxa-2,7-diazabicyclo[3.3.0]oct-1-ene

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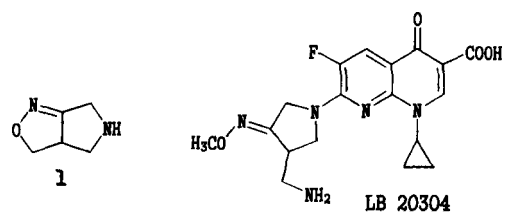
Since the discovery of nalidixic acid[1] in the early 1960s and norfloxacin[2] in 1980, many fluorinated pyridone carboxylic acids have been synthesized as antibacterial agents known collectively as the quinolones. In line with this effort, much attention has been focused on the introduction of an amino group such as piperazine and pyrrolidine moiety at the C-7 position of the quinolone ring system to develop broad-spectrum antibacterial activity. These amino groups display an important role in the control of potency, spectrum and pharmacokinetics of quinolone antibacterials and the structural modification of piperazine and pyrrolidine rings has been the target of intensive research activities worldwide.[3]

Recently, it has been reported that the introduction of an alkyloximino group in the pyrrolidine ring as an amino group surrogate showed enhanced antibacterial activity against Gram-positive strains.[4-6] Among these compounds, LB20304 which has 3-(methyloximino)-4-(aminomethyl)pyrrolidine as an amino substituent showed potent antimicrobial activity against both Gram-positive and Gram-negative organisms with improved pharmacokinetic profiles and is currently under clinical trial.[6]

As part of an ongoing effort to find potent quinolone antibacterial agents, we have investigated modifications of the C-7 substituent of the quinolone ring and LB20304 prompted us to synthesize bicyclic amines which have an oximino group in a cyclic structure. We disclose herein our preliminary results on the synthesis of 3-oxa-2,7-diazabicyclo[3.3.0]oct-1-ene **1**.

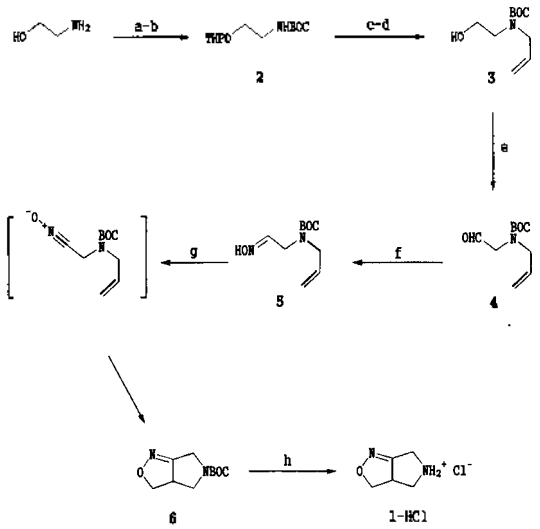
Synthesis of bicyclic amine **1** is outlined in *Scheme* 1.



1 LB 20304

Consecutive protections of ethanolamine were carried out using BOC_2O and DHP to give carbamate **2**. Reaction with allyl bromide/NaH in DMSO converted carbamate **2** to *N*-allylated product which was selectively deprotected to alcohol **3**. Among several oxidation methods, Swern oxidation[7] transformed alcohol **3** to unstable aldehyde **4** in high yield. Following oxime formation provided almost an equal isomeric mixture of syn and anti oximes **5**. *In situ* generation of nitrile oxide and subsequent intramolecular cycloaddition[8] produced bicyclic amine **6** that was finally deprotected to the target 3-oxa-2,7-diazabicyclo[3.3.0]oct-1-ene **1** as a HCl salt in moderate yield[9]. The synthetic pathway described above was quite efficient and is applicable to the synthesis of versatile analogues. Currently, the coupling reaction of the compound **1** with various quinolone cores, their biological assay of coupling products, and further modification of bicyclic amine **1** are actively under way.

Scheme 1. reagents and conditions: (a) BOC_2O, Et_3N, CH_2Cl_2, 80%; (b) DHP, cat. TsOH, 91%; (c) allyl bromide, NaH, DMSO, 85%; (d) cat. TsOH, MeOH, 96%; (e) Swern oxidation, 89%; (f) NH_2OH·HCl, Na_2CO_3, $EtOH/H_2O$, 91%; (g) NBS, Et_3N, DMF, 40%; (h) acetyl



chloride, MeOH, 98%.

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9. ^{1}H NMR(100MHz, $CDCl_3$, δ) Compound **3**: 1.46 (9H,s), 2.57(1H, s), 3.37(2H, t, J=5.4 Hz), 3.73(2H, t, J=5.4Hz), 3.86(2H, td, J=1.2, 5.5Hz), 5.06(1H, qd, J=1.5, 4.9Hz), 5.20(1H, q, J=1.5Hz), 5.62-5.98(1H, m); Compound **4**: 1.45(9H, s), 3.85-3.93(4H, m), 5.12(1H, br d, J=1.2Hz), 5.22(1H, br s), 5.68-5.98(1H, m), 9.57(1H, s); Compound **5**(major isomer): 1.46(9H, s), 3.75-3.93(4H, m), 5.02-5.12(1H, m), 5.30(1H, br s), 5.57-6.02(1H, m), 7.38(1H, t, J=5.6Hz); Compound **6**: 1.48(9H, s), 3.00-3.36(1H, m), 3.79-4.04(3H, m), 4.13(2H, br s), 4.47-4.66(1H, m); HCl salt of compound **1**(DMSO-d^6): 2.97-4.6(7H, series of m), 10.12(2H, br s).