A Convenient Synthesis of 1,2,4-Oxadiazolidine-3,5-dione

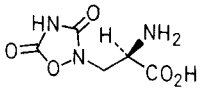
P. Renaut,* D. Thomas, F.D. Bellamy

Laboratoires Fournier, Centre de Recherche, 50 rue de Dijon, Daix, F-21121 Fontaine les Dijon, France

A convenient three-step synthesis of 1,2,4-oxadiazolidine-3,5-dione involving debenzylation of 3-benzyloxy-1,2,4-oxadiazol-5(4*H*)-one with boron tribromide is reported. By contrast with the two known procedures, this synthesis requires only nonhazardous and commercially available reagents.

1,2,4-Oxadiazolidine-3,5-dione is an important moiety in medicinal chemistry since it is considered as a bioisostere for the carboxylic acid group.[1] for example, quisqualic acid [**1**, (*R*)-2-amino-3-(3,5-dioxo-1,2,4-oxadiazolidin-2-yl)propanoic acid] a natural product extracted from *quisqualic fructus* has been shown to possess biological activities very similar to those of glutamic acid **2**.[2]

As it is the case for quisqualic acid **1**, other *N*-2-substituted 1,2,4-oxadiazolidine-3,5-diones may be synthesized through alkylation of the parent heterocycle **5**.[3,4] Zinner's group published two syntheses[5,6] of **5** but both procedures suffer severe drawbacks: one utilizes hydroxylamine base as a pure solid which may decompose explosively,[7] whereas the other involves not readily available 2-(tetrahydropyranyl)isocyanate.[8]



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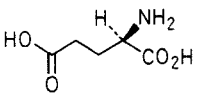

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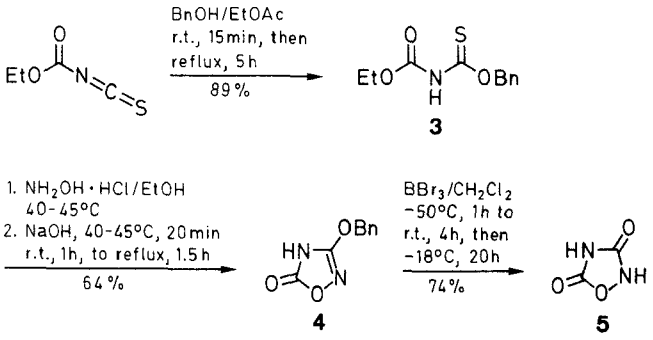
As part of our strategy directed toward the synthesis of new condensed heterocycles, a convenient preparation of **5** on a large scale was required. In this paper we describe a three-step sequence which does not involve any hazardous material (Scheme).

Our pivotal intermediate is the 3-benzyloxy derivative **4** which is readily prepared from commercial reagents and which we expected to be easily cleaved in order to give the target molecule **5**.

Addition of benzyl alcohol with ethyl isothiocyanatoformate[9] gives the carbamate **3** in 89% yield. This compound, upon reaction with hydroxylamine hydrochloride in the presence of potassium hydroxide[10] cyclizes to the oxadiazolone **4** in 64% yield.



Scheme

Table. Spectral Data for Compounds **3**, **4**, **5** Prepared

Compounds	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR[b] δ, J (Hz)	^{13}C-NMR[b] δ
3	$C_{11}H_{13}NO_3S$ (239.3)	3220, 1770	1.29 (t, 3H, J = 7), 4.22 (q, 2H, J = 7), 5.58 (s, 2H), 7.34–7.46 (m, 5H), 8.20 (brs, 1H)	14.1, 62.5, 73.9, 128.0, 128.5, 128.6, 134.4, 149.0, 188.0
4	$C_9H_8N_2O_3$ (192.2)	1790, 1610	5.28 (s, 2H), 7.42 (s, 5H)	72.3, 128.8, 129.4, 133.2, 159.2, 160.6
5	$C_2H_2N_2O_3$ (102.1)	1820, 1740	9.89 (brs)	154.4, 158.6

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.18, N ±0.23.

[b] Measured in: $CDCl_3$/TMS for **3**, **4**; DMSO-d_6/TMS for **5**.

All our attempts to remove the benzyl group of **4** by hydrogenolysis remained unsuccessful. We were also unable to carry out this deprotection via the chromic acid oxidation[11] to the corresponding benzoate. Finally, boron tribromide proved to be the reagent of choice and achieved this debenzylation in 74% yield.

We have carried out this synthesis in three steps, with a 42% overall yield on a multigram scale without any problem.

All reagents were of commercial quality: ethoxycarbonyl isothiocyanate, hydroxylamine hydrochloride and BBr_3 were purchased from Aldrich Chemical Co.; benzyl alcohol was purchased from Janssen Chemical Co. Reagent quality solvents were used without further purification. NMR spectra were recorded on a Bruker AC-P 300 spectrometer and IR spectra on a Perkin-Elmer 782 infrared spectrophotometer. Melting points were obtained using an Electrothermal® melting point apparatus and are uncorrected.

Ethyl *N*-(Benzyloxythiocarbonyl)carbamate (3):
BnOH (11.8 mL, 114 mmol) is added under N_2, dropwise, at r.t., over 15 min to a solution of ethyl isothiocyanatoformate (13.54 g, 103 mmol) in EtOAc (200 mL). After refluxing for 5 h the solvent is evaporated under reduced pressure. The crude yellow solid obtained is stirred with Et_2O (25 mL) for 2 h and placed at −18 °C overnight. The precipitated product **3** is isolated by suction and washed with hexane; yield: 21.9 g (89%); mp 93–95 °C (Lit.[9] mp 96 °C).

3-Benzyloxy-1,2,4-oxadiazol-5(4*H*)-one (4):
A suspension of compound **3** (21.5 g, 90 mmol) and hydroxylamine hydrochloride (9.25 g, 133 mmol) in EtOH 95% (400 mL) is stirred under N_2 and heated to 40–45 °C. To the resulting clear solution is added NaOH (5.70 g, 142 mmol) in small portions over a period of 20 min. A white solid precipitates. The mixture is stirred at r.t. for 1 h and heated slowly to the reflux of the solvent. This reflux is maintained for 1.5 h. The solvent is evaporated and the pasty residue is partitioned between H_2O and CH_2Cl_2. The aqueous layer is further extracted with two portions of EtOAc. The combined organic layers are washed with brine, dried (Na_2SO_4) and treated with charcoal. After filtration and evaporation the resulting solid (14 g) is recrystallized from a mixture of CH_2Cl_2 and hexane to afford **4** as a white solid (9.07 g); mp 109–112 °C (Lit.[10] mp 108–113 °C). The mother liquor is flash chromatographed on a silica gel column (15 × 4 cm, 70–230 mesh). Elution with cyclohexane/EtOAc (6:4) gives a second crop (2.01 g; mp 98–103 °C); total yield: 11.08 g (64%).

1,2,4-Oxadiazolidine-3,5-dione (5):
In a dried, Ar-filled three-necked round-bottom flask fitted with magnetic stirrer, thermometer and addition funnel, 3-benzyloxy-1,2,4-oxadiazol-5(4*H*)-one (**4**; 10.73 g, 55.9 mmol) is dissolved in CH_2Cl_2 stabilized with amylene (2-methyl-2-butene, 250 mL). A solution of BBr_3 (5.6 mL, 59.2 mmol) in CH_2Cl_2 (10 mL) is added dropwise at −50 °C over 30 min. The resulting mixture is maintained at −50 °C for 30 min, heated slowly to r.t. for 4 h and kept at −18 °C over 20 h. The mixture is then poured into iced water (60 mL) and extracted with Et_2O (1 × 250 mL, 4 × 100 mL). The organic layers are dried ($MgSO_4$), treated with charcoal, filtered and evaporated. The yellow pasty solid obtained is stirred with hexane (100 mL) for 30 min, the resulting white solid is filtered and washed with cold hexane (50 mL) to afford crude **5**. After dissolution of this compound in anhydrous Et_2O (250 mL), filtration of some insoluble material, hexane (250 mL) is added until cloudiness. The mixture is then concentrated to 100 mL under reduced pressure, cooled to 0 °C for 2 h. Filtration affords **5** as a white solid; yield: 4.2 g (74%); mp 108 °C. An analytical sample is obtained by recrystallization from *i*-Pr_2O/petroleum ether; mp 107–108 °C (Lit.[4] mp 107–108 °C).

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