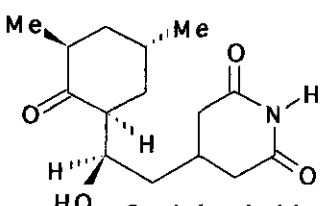
A MILD PREPARATION OF 2,6-PIPERIDINEDIONES

Jiarong Zhu,[1] Pham Huy Chuong,[2] Pascale Lemoine,[3] Alain Tomas[3], and Hervé Galons[1]*

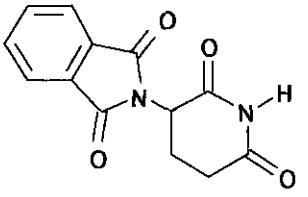
Laboratoires de [1]Chimie Organique, de [2]Toxicologie et de [3]Physique. Faculté de Pharmacie, 4, avenue de l'Observatoire 75270 Paris, France

Abstract - Substituted glutaric acids reacted with alkyloxyamines in the presence of *N*-ethyl-*N*-dimethylaminopropylcarbodiimide hydrochloride to form 1-alkyloxy-2,6-piperidinediones. The protecting group on the nitrogen was easily removed in high yield. This process is exemplified by the preparation of aminoglutethimide.

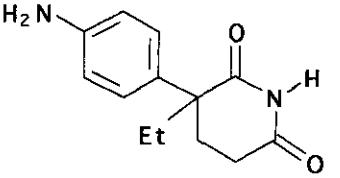
The 2,6-piperidinedione heterocycle (glutarimide) is present in a large number of biologically active compounds.[1-4] Cycloheximide is an antibiotic with complex biological activities.[1] The interest for the immuno-suppressor thalidomide is regularly growing.[2a] It is currently used for AIDS.[2b] Its activity against angiogenesis has been recently discovered.[2c] Aminoglutethimide[3a] is a competitive inhibitor of human placental aromatases which is widely used in the treatment of estrogenic dependent cancers.[3b] Recently, 3-aminoglutarimide was introduced into a peptide chain to prepare an enzyme inhibitor.[4]



Cycloheximide



Thalidomide

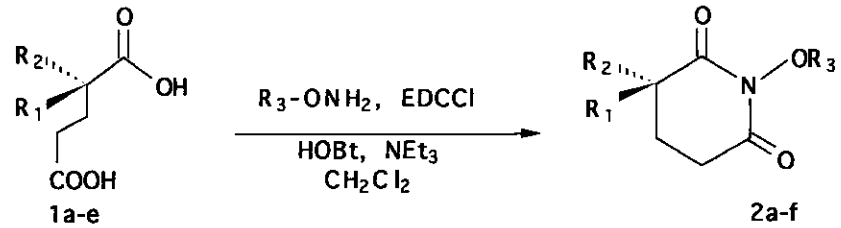


Aminoglutethimide

Piperidine-2,6-diones are usually obtained by heating δ-dinitriles in an acidic solution.[5] Owing to the harsh classical conditions, a milder method was proposed. It involves the cyclisation of an activated acid group with an amide upon moderate heating.[6] This reaction does not proceed at room temperature and the preparation of a monoamide from a diacidic compounds requires multi-step procedures.

We have recently observed another access to piperidinedione derivatives. It relies on the condensation of benzyloxyamine with Boc-glutamic α-phenyl ester to give a *N*-benzyloxypiperidinedione derivative.[7] We wish to report that a glutarimide ring could be formed rapidly at or below room temperature when benzyloxyamine (Bzl-ONH_2) or trityloxyamine (Trt-ONH_2) directly reacted with δ–diacid in the

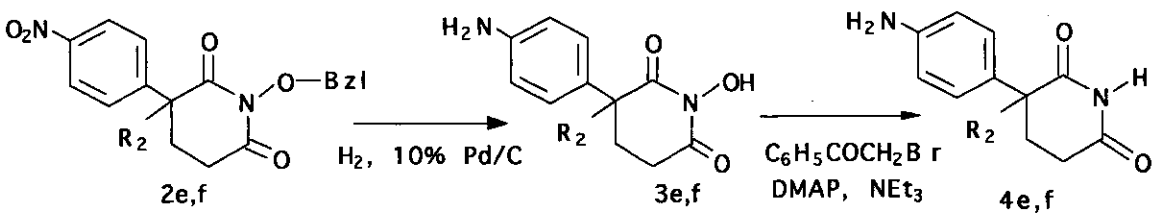
benzyloxyamine (Bzl-ONH_2) or trityloxyamine (Trt-ONH_2) directly reacted with δ–diacid in the presence of *N*-ethyl-*N*-dimethylaminopropylcarbodiimide hydrochloride (EDCCl) and *N*-hydroxybenzotriazole (HOBt). Diisopropylcarbodiimide also allowed the condensation but the reaction failed when dicyclohexylcarbodiimide was used.



1a-e 2a-f

Compound	R_1	R_2	R_3	Yield(%)
2a	Me	Me	Bzl	72
2b	Me	Me	Trt	56
2c (S)	H	BocNH	Bzl	81
2d (R)	BocNH	H	Bzl	75
2e (R,S)	Me	4-O_2N-Phe	Bzl	73
2f (R,S)	Et	4-O_2N-Phe	Bzl	81

The present method provides an expeditious asymmetric synthesis to the precursors (**2c,d**) of thalidomide. These intermediates were obtained in higher yield than with the previously described process.[7] Racemic 1-benzyloxy-3-alkyl-3-(4-nitrophenyl)-2,6-piperidinediones (**2e,f**) were converted in two steps into **4e,f**. Reductions of the nitro group and debenzylation were simultaneously achieved. The aromatic amino group was not affected during the mild elimination of the hydroxyl group. In ^{13}C nmr, a 5 ppm downfield shift of the C=O groups resulted from the elimination of the hydroxyl group.



2e,f 3e,f 4e,f

In conclusion we have shown that the enhancement of the nucleophilicity by introduction of alkyloxy group on nitrogen greatly facilitates acylations. These groups were stable during the condensation and the deprotection step was easy.

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EXPERIMENTAL

Nmr spectra were recorded on a 270 MHz Bruker spectrometer.

General method of the preparation of 1-alkyl-3,3-disubstituted piperidine-2,6-diones (2a-f). EDCCl (1.286 g, 6.37 mmol) was added at 0°C to a mixture of 2,2-dimethylglutaric acid (0.500 g, 3.06 mmol), benzyloxyamine (0.452 g, 3.67 mmol), 1-hydroxybenzotriazole (0.908 g, 6.73 mmol), and triethylamine (1.545 g, 15.30 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred overnight and allowed the temperature rise to room temperature. Then, the solvent was removed, and ethyl acetate was added. The mixture was washed with saturated $NaHCO_3$ solution, 10% citric acid solution, and water, respectively, and the organic layer was dried over Na_2SO_4. The crude product was purified on a column of silica gel. Eluents : **2a,e,f** : CH_2Cl_2; **2b** : CH_2Cl_2/C_6H_{12} 2:1; **2c,d** : CH_2Cl_2/AcOEt 1:1.

1-Benzyloxy-3,3-dimethylpiperidine-2,6-dione (2a). Oil. ^1H Nmr ($CDCl_3$) δ 1.20 (s, 6H), 1.70 (t, J = 7.9 Hz, 2H), 2.70 (t, J = 7.9 Hz, 2H), 5.05 (s, 2H), 7.42 (m, 3H), 7.55(m, 2H). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.02; H, 6.88; N, 5.67. Found; C, 68.22; H, 7.01; N, 5.91.

1-Trityloxy-3,3-dimethylpiperidine-2,6-dione (2b). mp 194-198 °C(cyclohexane). ^1H Nmr ($CDCl_3$) δ 1.30 (s, 6H), 1.90 (t, J = 7.9 Hz, 2H), 2.70 (t, J = 7.9 Hz, 2H), 7.30 (br s, 15H). Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.19; H, 6.26; N, 3.51. Found; C, 78.06; H, 6.49; N, 3.43.

(S)-1-Benzyloxy-3-*tert*-butyloxycarbonylaminopiperidine-2,6-dione (2c), (R)-1-Benzyloxy-3-*tert*-butyloxycarbonylaminopiperidine-2,6-dione (2d). 2c : mp 148-151 °C(isopropanol), (lit.,[7] 150 °C). $[\alpha]_D$ = - 3.9° (c = 1.0, MeOH). **2d** : mp 150-151 °C(isopropanol), $[\alpha]_D$ = + 3.9° (c = 1.0, MeOH).

1-Benzyloxy-3-methyl-3-(4-nitrophenyl)piperidine-2,6-dione (2e). Oil. ^1H Nmr ($CDCl_3$) δ: 1.50(s, 3H), 2.10(m, 1H), 2.40(m, 2H), 2.70(m, 1H), 5.10 (s, 2H), 7.20(d, J = 6.5 Hz, 2H), 7.45(m, 5H), 8.23(d, J = 6.5 Hz, 2H). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.08; N, 7.91. Found; C, 64.11; H, 5.32; N, 7.69.

1-Benzyloxy-3-ethyl-3-(4-nitrophenyl)piperidine-2,6-dione (2f). Oil. ^1H Nmr ($CDCl_3$) δ : 0.85(t, J = 7.9 Hz, 3H), 1.86-2.10 (m, 5H), 2.10-2.50(m, 3H), 2.78(dt, J = 12 Hz, J = 2 Hz, 1H), 4.97(d, J = 10 Hz, 1H), 5.05(d, J = 10 Hz, 1H), 7.20-7.40(m, 5H), 7.35(d, J = 6.5 Hz, 2H), 8.20(d, J = 6.5 Hz, 2H); ^{13}C nmr δ : 7.1, 24.1, 29.2, 32.3, 51.4, 78.2, 122.0, 126.2, 127.3, 128.4, 129.5, 133.2, 148.5, 149.3, 165.2, 170.1. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.43; N, 7.61. Found; C, 65.45; H, 5.34; N, 7.33.

General procedure for the obtention of *N*-hydroxypiperidinediones. Compound (**2e**) (1.066 g, 3.01 mmol) was dissolved in 50 ml of methanol and 10% Pd/C (0.10 g) was added. The suspention was stirred for 2 h under hydrogen, filtered, and concentred in vacuo. The crude products were recrystallized.

1-Hydroxy-3-methyl-3-(4-aminophenyl)piperidine-2,6-dione (3e). mp 189 °C(CH_2Cl_2). ^{1}H Nmr ($CDCl_3$) δ : 1.60 (s, 3H), 2.20 (m, 2H), 2.60 (m, 2H), 4.90(br s, 2H), 6.63(d, *J* = 6.5 Hz, 2H), 6.94(d, *J* = 6.5 Hz, 2H); ^{13}C nmr δ : 24.1 , 27.8, 32.0, 45.4, 113.8, 126.0, 127.5, 145.0, 164.3, 169.0. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 5.98; N, 11.97. Found; C, 61.33; H, 5.76; N, 12.23.

1-Hydroxy-3-ethyl-3-(4-aminophenyl)piperidine-2,6-dione (3f). mp 92 °C(CH_2Cl_2). ^{1}H Nmr ($CDCl_3$) δ : 0.90 (t, *J* = 7.9 Hz, 3H), 1.95 (m, 2H), 2,23(m, 2H), 2,80(m, 2H), 4.70 (br s, 2H), 6.65 (d, *J* = 6.5 Hz, 2H), 6.92(d, *J* = 6.5 Hz, 2H); ^{13}C nmr δ : 6.95, 24.3, 27.15, 31.3, 49.4, 113.5, 125.0, 126.5, 143.8, 164.5, 168.8. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.90; H, 6.45; N, 11.29. Found; C, 63.06; H, 6.65; N, 11.02.

General procedure for the obtention of piperidinediones. A solution of **3e** (0.495 g, 2.10 mmol), triethylamine (0.29 g, 2.10 mmol), bromoacetophenone (0.418 g, 2.10 mmol) and DMAP (0.025 g, 0.21 mmol) in acetonitrile (15 ml) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the crude products were purified by recrystallization.

3-Methyl-3-(4-aminophenyl)piperidine-2,6-dione (4e). mp 142-144 °C(ethyl acetate). ^{1}H Nmr ($CDCl_3$) δ 1.60(s, 3H), 2.10-2.60(m, 4H), 3.70(br s, 2H), 6.62(d, *J* = 6.5 Hz, 2H), 6.98(d, *J* = 6.5 Hz, 2H), 7.80(br s, 1H); ^{13}C nmr δ : 24.9, 27.6, 30.0, 44.7, 112.9, 124.8, 127.0, 143.8, 170.9, 174.4.

3-Ethyl-3-(4-aminophenyl)piperidine-2,6-dione (4f) (aminogluthetimide). mp 150-153 °C(ethyl acetate) (lit.,[3] 152-154 °C).

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