Synthesis of Bicyclic 1,3,5-Triazine-2,4(3*H*)-diones: Reaction of Amidines with Diphenyl Iminodicarboxylate

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The preparation of bicyclic 1,3,5-triazine-2,4(3*H*)-diones **3** has been investigated. Diphenyl iminodicarboxylate (**2**) reacted smoothly with cyclic amidines to give bicyclic triazinediones in good yields.

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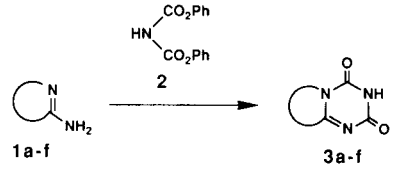
We have reported that 6,7,8,9-tetrahydro-2*H*-pyrido[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (**3a**) is an important moiety of the compounds with 5-HT_2 antagonist activity [1]. A number of methods have been developed for the preparation of bicyclic 1,3,5-triazine-2,4(3*H*)-diones. A typical method involves the treatment of 2-aminopyridine (**1e**) with ethoxycarbonyl isocyanate followed by successive cyclization of the resulting adduct to give 2*H*-pyrido[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (**3e**) [2,3]. More recently, there has been another method which consists of the reaction of **1e** with chlorocarbonyl isocyanate followed by treatment with triethylamine affording **3e** in good yield [4]. However, an attempt to prepare the corresponding 6,7,8,9-tetrahydro analogue **3a** by treatment of 2-amino-3,4,5,6-tetrahydropyridine (**1a**), an aliphatic amidine, with chlorocarbonyl isocyanate was unsuccessful because it gave a mixture of unknown products. We, therefore, prepared **3a** by the reaction of **1a** with phenoxycarbonyl isocyanate in 57% yield [1]. Since the above isocyanates were not very convenient because they could not be stored for a long period at room temperature, we investigated more useful reagents applicable for the reaction with the aliphatic amidine **1a**. Reaction of **1a** with diphenyl iminodicarboxylate (**2**) [5] in acetonitrile at room temperature afforded **3a** in 79% yield (Scheme). Thus, we have found that reagent **2** is effective to prepare **3a** and is stable at room temperature for over a year.

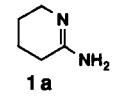
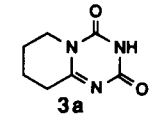
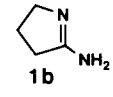
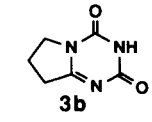
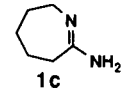
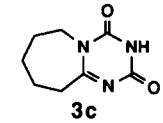
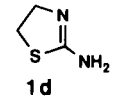
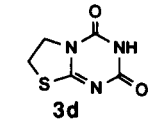
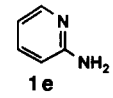
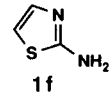
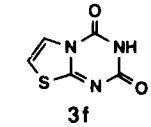
Scheme



In order to evaluate the scope of the method, we investigated the reaction of **2** with other amidines (Scheme and Table). The reaction with aliphatic amidines **1b-d** with **2** in acetonitrile at room temperature gave **3b-d** in good yields. In the case of the aromatic amidines **1e-f**, higher temperature and a longer reaction time were required to obtain **3e-f**. On the other hand, reaction of 2-aminopyrimidine with **2** did not give the corresponding bicyclic product presumably due to its weak nucleophilicity.

Table

Reaction of 2 with Amidines

Amidine	Reaction Time (h)	Product	Yield (%)
 **1a**	2	 **3a**	79
 **1b**	3	 **3b**	77
 **1c**	2.5	 **3c**	79
 **1d**	2	 **3d**	91
 **1e**	5	 **3e**	73
 **1f**	4.5	 **3f**	75

In conclusion, diphenyl iminodicarboxylate (**2**) is a stable and useful reagent for the preparation of bicyclic 1,3,5-triazine-2,4(3*H*)-diones.

EXPERIMENTAL

All melting points were determined with a Büchi 520 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 spectrometer. Proton nuclear magnetic resonance spectra were recorded with JEOL JNM-FX-90Q spectrometer using tetramethylsilane as the internal standard. Mass spectra were measured on a JEOL JMS-HX100 instrument.

Diphenyl Iminodicarboxylate (**2**).

This compound was prepared by the reported procedure [5], from phenol (9.41 g, 0.10 mole) and chlorocarbonyl isocyanate (5.27 g, 50 mmoles) in 86% yield (11.0 g), mp 118-120° (toluene), (lit [5], mp 124-126°); ir (potassium bromide): 3272, 1792, 1732, 1596, 1490 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45. Found: C, 65.55; H, 4.22; N, 5.47.

General Procedure for the Reaction of Aliphatic Amidines **1a-d** with Diphenyl Iminodicarboxylate (**2**).

The aliphatic amidine hydrochloride **1a-d** (15 mmoles) was added to *N*-ethanolic sodium ethoxide (15 ml, 15 mmoles) and the mixture was stirred at room temperature for 30 minutes, then the precipitated sodium chloride was filtered through a Celite pad. The filtrate was concentrated to dryness *in vacuo*. After the residue was dissolved in acetonitrile (30 ml), diphenyl iminodicarboxylate (**2**) (3.86 g, 15 mmoles) was added, and the mixture was stirred at room temperature for appropriate periods of time (Table). The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column (15 cm x 4 cm; 70-230 mesh) using 4-5% methanol in chloroform as the eluent to give the 1,3,5-triazine-2,4(3*H*)-diones **2a-d**.

6,7,8,9-Tetrahydro-2*H*-pyrido[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (**3a**).

This compound was obtained from 2-amino-3,4,5,6-tetrahydropyridine hydrochloride (**1a**) [6] and **2** as colorless crystals, mp 185-187° (ethanol), yield 79%; ir (potassium bromide): 3450, 3200, 3070, 1700, 1590, 1490 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 1.6-1.9 (4H, m, CH_2 x 2), 2.65 (2H, t, CH_2), 3.64 (2H, t, CH_2), 11.39 (1H, br s, NH) ppm; ms: m/z 167 (M^+).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.30; H, 5.43; N, 25.14. Found: C, 50.37; H, 5.45; N, 24.91.

7,8-Dihydro-6*H*-pyrrolo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (**3b**).

This compound was obtained from 2-amino-1-pyrroline hydrochloride **1b** [6] and **2** as colorless crystals, mp 199-201° (ethanol), yield 77%; ir (potassium bromide): 3430, 3210, 3080, 1740, 1710, 1690, 1630 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 2.07 (2H, m, CH_2), 2.87 (2H, t, CH_2), 3.82 (2H, t, CH_2), 11.25 (1H, br s, NH) ppm; ms: m/z 153 (M^+).

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 46.90; H, 4.65; N, 27.13.

7,8,9,10-Tetrahydro-6*H*-1,3,5-triazino[1,2-*a*]azepine-2,4(3*H*)-dione (**3c**).

This compound was obtained from 7-amino-3,4,5,6-tetrahydro-2*H*-azepine hydrochloride **1c** [7,8] and **2** as colorless crystals, mp 157-158° (ethyl acetate), yield 79%; ir (potassium bromide): 3520, 3200-2800, 1730, 1670, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): 1.7 (6H, m, CH_2 x 3), 2.8 (2H, m, CH_2), 4.0 (2H, m, CH_2), 11.0 (1H, br s, NH) ppm; ms: m/z 181 (M^+).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.04; H, 6.21; N, 23.32.

6,7-Dihydro-2*H*-thiazolo[3,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (**3d**).

This compound was obtained from 2-aminothiazoline hydrochloride (**1d**) and **2** as colorless crystals, mp 233-235° (ethanol), yield 91%; ir (potassium bromide): 3450, 3030, 1740, 1695, 1575 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 3.51 (2H, dd, CH_2), 4.22 (2H, dd, CH_2), 11.27 (1H, br s, NH) ppm; ms: m/z 171 (M^+).

Anal. Calcd. for $C_5H_5N_3O_2S$: C, 35.09; H, 2.94; N, 24.55; S, 18.93. Found: C, 35.16; H, 2.89; N, 24.65; S, 18.73.

General Procedure for the Reaction of Aromatic Amidines **1e-f** with Diphenyl Iminodicarboxylate (**2**).

A mixture of the aromatic amidine **1e-f** (15 mmoles) and **2** (3.86 g, 15 mmoles) in 1,4-dioxane (30 ml) was refluxed for appropriate periods of time (Table). After cooling, the mixture was concentrated *in vacuo*. The resulting precipitates were collected by filtration and recyrstallized from the appropriate solvent to give the 1,3,5-triazine-2,4(3*H*)-diones **3e-f**.

2*H*-Pyrido[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (**3e**).

This compound was obtained from 2-aminopyridine (**1e**) and **2** as colorless crystals, mp 208-211° (methanol), (lit [4], mp 203-206°), yield 73%; ir (potassium bromide): 3450, 3080, 2980, 1755, 1660, 1640 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 6.95 (2H, m), 7.80 (1H, ddd), 8.38 (1H, d), 11.82 (1H, br s, NH) ppm; ms: m/z 163 (M^+).

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.54; H, 2.71; N, 25.67.

2*H*-Thiazolo[3,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (**3f**).

This compound was obtained from 2-aminothiazole (**1f**) and **2** as pale yellow crystals, mp >280° (*N,N*-dimethylformamide), yield 75%; ir (potassium bromide): 3240, 3065, 1755, 1740, 1680, 1640, 1570 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 7.12 (1H, d), 7.66 (1H, d), 11.67 (1H, br s, NH), ppm; ms: m/z 169 (M^+).

Anal. Calcd. for $C_5H_3N_3O_2S$: C, 35.50; H, 1.79; N, 24.84; S, 18.95. Found: C, 35.63; H, 1.96; N, 24.57; S, 18.81.

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