Retro-Ene Reactions in Heterocyclic Synthesis. V. A Novel Synthetic Method for 1,3,5-Triazine-2,4(1*H*,3*H*)-diones

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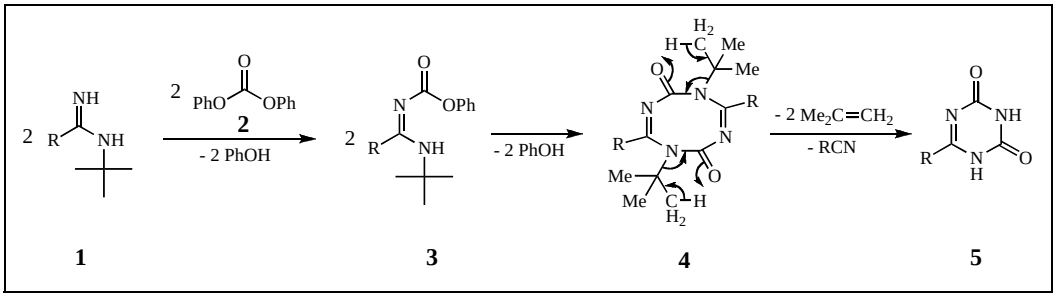

N-t-Butylamidines **1** on heating with diphenyl carbonate (**2**) at 150-180° gave the 1,3,5-triazine-2,4(1*H*,3*H*)-dione derivatives **5**. Acylation of amidines **1** and cyclocondensation of the resulting carbamates **3** gave [1,3,5,7]tetrazocine-2,6-dione derivatives **4**, and subsequent retro-ene reaction and ring contraction afforded triazine derivatives **5**.

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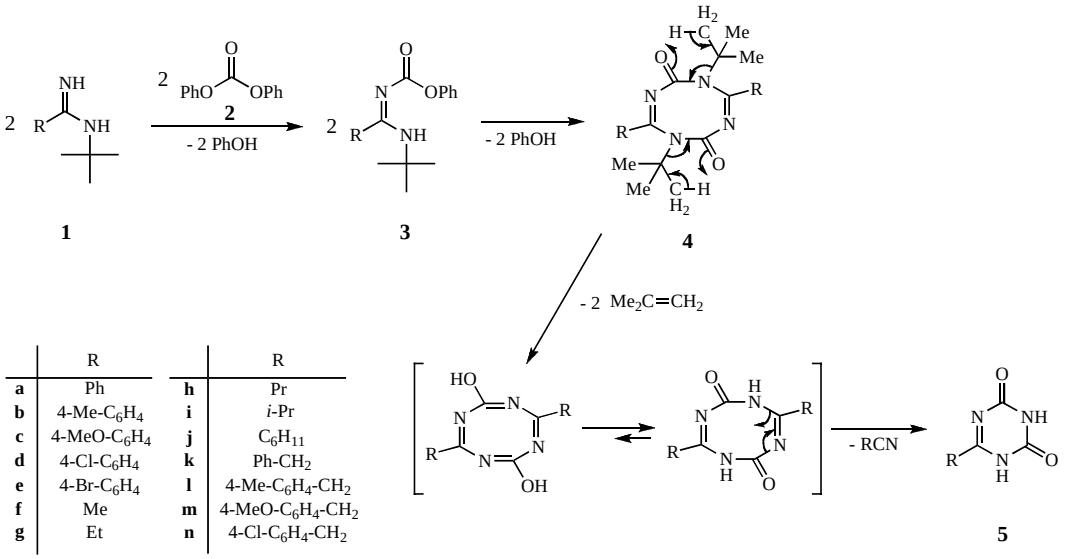
We previously reported synthetic methods for a variety of heterocyclic compounds *via* sterically assisted retro-ene reactions [1-4]. In the fourth paper in this series, we reported a convenient synthesis of 6-aryl-substituted 1,3,5-triazine-2,4(1*H*,3*H*)-diones from amidines and diphenyl imidodicarboxylate [4]. This report deals with a new and interesting synthetic method for 1,3,5-triazine-2,4(1*H*,3*H*)-dione derivatives.

The addition of a solution of *N-t*-butylbenzamidine (**1a**) in benzene to a stirred solution of diphenyl carbonate (**2**) in benzene, with stirring for 1 hour at room temperature, gave the *N*-acylated product phenyl (*t*-butylamino)-phenylmethylenecarbamate (**3a**) in 96% yield. A solution of carbamate **3a** in tetraglyme was heated in an oil bath at 180° for 5 hours; after the removal of low boiling materials and solvent under reduced pressure, 6-phenyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**5a**) was obtained in 83% yield. Scheme 1 shows the mechanism for the reaction. On heating at 180°, **3a** underwent cyclocondensation to form [1,3,5,7]tetrazocine-2,6-dione derivative **4a**, which subsequently underwent a retro-ene reaction with elimination of 2-methylpropene and a ring contraction reaction with elimination of benzonitrile to afford triazine derivative **5a**. The structures of **3a** and **5a** were confirmed on the basis of elemental analysis and spectral data. 2-Methylpropene eliminated during the reaction was collected by trapping generated gases (83 %), and was identified by agreement with spectral data from the literature [5,6]. The elimination of nitrile was confirmed by isolation of benzonitrile *via* redistillation of the low boiling materials (78 %). Although the intermediate tetrazocine derivative **4a** could not be isolated, the characterization of these by-products supports the contention that the reaction mechanism is as shown in Scheme 1. It seems that steric strain between the *t*-butyl and phenyl groups in the intermediate tetrazocine derivative **4a** is an important factor in the easy elimination of 2-methylpropene, as described in our previous papers [1,2,4].

Synthesis of 6-phenyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**5a**) was also successfully carried out in a one-pot procedure in which a solution of amidine **1a** in diglyme was gradually added to a stirred solution of **2** in diglyme at room temperature during 10 monutes, followed by heating under reflux in a 180° oil bath for 5 hours. After work up as described in experimental section, triazine derivative **5a** was obtained in 83% yield. Similarly, various *N-t*-butylamidines **1** were allowed to react with diphenyl carbonate (**2**) by means of one-pot procedure under the reaction conditions indicated in Table 1; the results obtained are summarized in Table 1.

The present method offers a facile synthetic route to a variety of 6-aryl and 6-alkyl-substituted 1,3,5-triazine-2,4(1*H*,3*H*)-dione derivatives. Ready availability of starting materials, experimental simplicity and satisfactory yields contribute to the usefulness of this method.

Scheme 1



	R		R
a	Ph	**h**	Pr
b	4-Me-C_6H_4	**i**	*i*-Pr
c	4-MeO-C_6H_4	**j**	C_6H_{11}
d	4-Cl-C_6H_4	**k**	Ph-CH_2
e	4-Br-C_6H_4	**l**	4-Me-C_6H_4-CH_2
f	Me	**m**	4-MeO-C_6H_4-CH_2
g	Et	**n**	4-Cl-C_6H_4-CH_2

Table 1

Preparation of Compounds **5**

Compd.	R	Reaction Temp [°C]	Reaction Time [h]	Yield [%]
5a	Ph	180	5	83
5b	4-Me-C_6H_4	180	5	83
5c	4-MeO-C_6H_4	180	5	85
5d	4-Cl-C_6H_4	150	8	84
5e	4-Br-C_6H_4	150	8	85
5f	Me	180	5	82
5g	Et	180	5	82
5h	Pr	180	5	84
5i	*i*-Pr	180	5	80
5j	C_6H_{11}	180	5	65
5k	Ph-CH_2	180	5	57
5l	4-Me-C_6H_4-CH_2	150	9	53
5m	4-MeO-C_6H_4-CH_2	150	9	43
5n	4-Cl-C_6H_4-CH_2	180	5	71

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Horiba FT-720 spectrometer in potassium bromide pellets. The ^{1}H nmr data were obtained with a JEOL JNM-ECX500M (500 MHz) spectrometer in deuteriodimethyl sulfoxide by using tetramethylsilane (0.03 %) as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP5050A spectrometer at 70 eV of ionization energy by use of a direct-inlet system. Elemental analyses were performed by using a Perkin-Elmer 2400 II CHN Analyzer.

N-t-Butylamidines **1** were prepared by the method of Cooper and Partridge [7]. Diphenyl carbonate (**2**) was commercially available and used without further purification.

Phenyl (*t*-Butylamine)phenylmethylenecarbamate (3a). To a stirred solution of diphenyl carbonate (**2**) (21.45 g, 100 mmoles) in benzene (200 ml) at room temperature was added a solution of *N-t*-butylbenzamidine (**1a**) (17.63 g, 100 mmoles) in benzene (200 ml) during 30 minutes. The mixture was stirred for an additional 1 hour at room temperature. Then the reaction mixture was shaken with 0.5 *M* aqueous sodium hydroxide solution (200 ml). The benzene layer was separated and washed with water (100 ml), dried over anhydrous sodium sulfate, and concentrated. The resulting residue was cooled, and the precipitated crystals were collected and washed with small amount of hexane to give 28.51 g (96 %) of carbamate **3a** as a colorless powder, mp 115.4-117.2°. A sample was recrystallized from methanol for analysis; mp 117.0-117.5°; ir 3319, 3294, 1674, 1589, 1575, 1549, 1493 cm^{-1}; ^{1}H nmr: δ 1.41 (9H, s, $C(CH_3)_3$), 6.79 (2H, d, J=7.5 Hz, aromatic), 7.11 (1H, t, J=7.5 Hz, aromatic), 7.28 (2H, t, J=7.5Hz, aromatic), 7.44–7.51 (5H, m, aromatic), 7.88 (1H, brs, NH); ms: (CI) m/z 297 (MH^+). *Anal*. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.13; H, 6.82; N, 9.41.

Conversion to 1,3,5-Triazine-2,4(1*H*,3*H*)-dione Derivative 5a of Carbamate 3a. A solution of carbamate **3a** (17.78 g, 60.0 mmoles) in tetraglyme (120 ml) was heated with stirring in 180° oil bath for 5 hours. The eliminated 2-methylpropene during the reaction was captured by means of the cooled (-60°) trap connected to the top of the condenser by the rubber tube. After concluding the heating, 2.80 g of volatile liquid was collected, and its ^{1}H nmr and ms spectral data were identical with those from literature on the 2-methylpropene [5,6]. The yield of 2-methylpropene was 83 %. The reaction mixture was distilled under reduced pressure after low-boiling fraction of bp 80-120° (2.5 mmHg) was collected solvent was removed. The residual solid was triturated with ether (10 ml) and was collected by filtration, giving 4.69 g of 1,3,5-triazine-2,4(1*H*,3*H*)-dione derivative **5a** (83 %), mp 288° dec. To a cooled low-boiling fraction were added ether (60 ml) and 1 *M* aqueous sodium hydroxide solution (60 ml) and the mixture was vigorously shaken. The ether layer was separated and the aqueous layer was extracted with ether (2x30 ml). The combined extracts were dried over anhydrous sodium sulfate, concentrated, and redistilled through a 50-cm spinning band column, giving 2.40 g of benzonitrile, bp 95-98° (35 mmHg). The collected benzonitrile was confirmed by direct comparison with ir and ^{1}H nmr spectral data of an authentic sample. The yield of benzonitrile was 78 %.

1,3,5-Triazine-2,4(1*H*, 3*H*)-diones 5. To a stirred solution of diphenyl carbonate (**2**) (20.0 mmoles) in diglyme (20 ml) at room temperature was added dropwise a solution of *N*-*t*-butylamidines **1** (20.0 mmoles) in diglyme (20 ml) during 10 minutes. The mixture was heated with stirring at the temperature indicated in Table 1. The reaction mixture was cooled, and the precipitated product was collected by filtration and washed with ether (10 ml). Evaporation of the combined filtrate under reduced pressure and washing the residual solid with ether (5 ml) gave an additional amount of product. All the products **5** obtained were of satisfactory purity as judged by ^{1}H nmr spectroscopy. Samples for analysis were recrystallized from dimethylformamide.

6-Phenyl-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5a). This compound was obtained as a colorless powder, mp 288° dec (reference [4], mp 290° dec); ir: 3178, 3132, 1728, 1676, 1603, 1566, 1483, 1400 cm^{-1}; ^{1}H nmr: δ 7.56 (2H, dd, J=8.3,7.5 Hz, aromatic), 7.67 (1H, t, J=7.5 Hz, aromatic), 8.09 (2H, d, J=8.3 Hz, aromatic), 11.40 and 12.42 (each 1H, brs, NH); ms: (CI) m/z 190 (MH^+).

6-(4-Methylphenyl)-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5b). This compound was obtained as a colorless powder, mp 305° dec (reference [4], mp 310.5° dec); ir: 3227, 3151, 1741, 1670, 1595, 1560, 1485, 1408 cm^{-1}; ^{1}H nmr: δ 2.40 (3H, s, CH_3), 7.36 and 8.01 (each 2H, d, J=8.6 Hz, aromatic), 11.34 and 12.30 (each 1H, brs, NH); ms: (CI) m/z 204 (MH^+).

6-(4-Methoxyphenyl)-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5c). This compound was obtained as a colorless powder, mp 304.5° dec; ir: 3246, 3163, 1718, 1697, 1595, 1558, 1473, 1398 cm^{-1}; ^{1}H nmr: δ 3.86 (3H, s, OCH_3), 7.10 and 8.12 (each 2H, d, J=8.7 Hz, aromatic), 11.28 and 12.23 (each 1H, brs, NH); ms: (CI) m/z 220 (MH^+). *Anal.* Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.81; H, 4.07; N, 19.39.

6-(4-Chlorophenyl)-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5d). This compound was obtained as a colorless powder, mp 312.5° dec (reference [4], mp 318° dec); ir: 3167, 3130, 1741, 1675, 1593, 1556, 1477, 1412 cm^{-1}; ^{1}H nmr: δ 7.64 and 8.10 (each 2H, d, J=8.9 Hz, aromatic), 11.42 and 12.47 (each 1H, brs, NH); ms: (CI) m/z 224 (MH^+).

6-(4-Bromophenyl)-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5e). This compound was obtained as colorless needles, mp 320° dec (reference [4], mp 325.5° dec); ir: 3219, 3167, 1743, 1670, 1595, 1558, 1477, 1406 cm^{-1}; ^{1}H nmr: δ 7.83 and 8.01 (each 2H, d, J=8.5 Hz, aromatic), 11.42 and 11.97 (each 1H, brs, NH); ms: (CI) m/z 268 and 270 (MH^+).

6-Methyl-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5f). This compound was obtained as a pale yellow powder, mp 275.5° dec (reference [8], mp 273-275° dec); ir: 3215, 3130, 1774, 1691, 1587, 1498, 1402 cm^{-1}; ^{1}H nmr: δ 2.15 (3H, s, CH_3), 11.18 and 12.05 (each 1H, brs, NH); ms: (CI) m/z 128 (MH^+).

6-Ethyl-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5g). This compound was obtained as a colorless powder, mp 209-210°; ir: 3138, 1751, 1672, 1599, 1500, 1415 cm^{-1}; ^{1}H nmr: δ 1.12 (3H, t, J=7.4 Hz, CH_3), 2.42 (2H, q, J=7.4 Hz, CH_2), 11.07 and 12.00 (each 1H, brs, NH); ms: (CI) m/z 142 (MH^+). *Anal.* Calcd. for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.19; H, 4.89; N, 29.89.

6-Propyl-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5h). This compound was obtained as colorless needles, mp 214.5-216°; ir: 3211, 3138, 1769, 1676, 1597, 1508, 1319 cm^{-1}; ^{1}H nmr: δ 0.91 (3H, t, J=7.4 Hz, CH_3), 1.64 (2H, sex, J=7.4 Hz, CH_2), 2.39 (2H, t, J=7.4 Hz, CH_2), 11.19 and 12.00 (each 1H, brs, NH); ms: (CI) m/z 156 (MH^+). *Anal.* Calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.72; H, 5.98; N, 27.20.

6-Isopropyl-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5i). This compound was obtained as a colorless powder, mp 246.5° dec; ir: 3209, 3134, 1759, 1674, 1599, 1508, 1425 cm^{-1}; ^{1}H nmr: δ 1.14 (6H, d, J=7.0 Hz, $2CH_3$), 2.66 (1H, sep, J=7.0 Hz, CH), 11.19 and 12.00 (each 1H, brs, NH); ms: (CI) m/z 156 (MH^+). *Anal.* Calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.08; H, 5.70; N, 27.21.

6-Cyclohexyl-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5j). This compound was obtained as colorless needles, mp 310° dec; ir: 3132, 1755, 1676, 1595, 1500, 1423 cm^{-1}; ^{1}H nmr: δ 1.18, 1.21, 1.25 (each 1H, t, J=12.6 Hz, C_6H_{11}), 1.41 (1H, td, J=12.0, 2.3 Hz, C_6H_{11}), 1.44 (1H, td, J=12.6, 2.9 Hz, C_6H_{11}), 1.65 (1H, d, J=11.5 Hz, C_6H_{11}), 1.75 and 1.81 (each 2H, d, J=12.6 Hz, C_6H_{11}), 2.37 (1H, tt, J=12.0, 3.4 Hz, C_6H_{11}), 11.17 and 11.93 (each 1H, brs, NH); ms: (CI) m/z 196 (MH^+). *Anal.* Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.50; H, 6.81; N, 21.50.

6-Benzyl-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5k). This compound was obtained as a light beige powder, mp 242.5° dec (reference [8], mp 254-255°); ir: 3154, 1757, 1673, 1589, 1500, 1423 cm^{-1}; ^{1}H nmr: δ 3.74 (2H, s, CH_2), 7.25 - 7.34 (5H, m, aromatic), 11.26 and 12.29 (each 1H, brs, NH); ms: (CI) m/z 204 (MH^+).

6-(4-Methylbenzyl)-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5l). This compound was obtained as a light beige powder, mp 267.5° dec; ir: 3126, 1753, 1670, 1593, 1500, 1423 cm^{-1}; ^{1}H nmr: δ 2.28 (3H, s, CH_3), 3.68 (2H, s, CH_2), 7.14 and 7.22 (each 2H, d, J=8.0 Hz, aromatic), 11.25 and 12.26 (each 1H, brs, NH); ms: (CI) m/z 218 (MH^+). *Anal.* Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.86; H, 5.24; N, 19.53.

6-(4-Methoxybenzyl)-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5m). This compound was obtained as a colorless powder, mp 238.5° dec; ir: 3228, 1763, 1736, 1695, 1591, 1514, 1400 cm^{-1}; ^{1}H nmr: δ 3.66 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 6.90 and 7.26 (each 2H, d, J=8.6 Hz, aromatic), 11.24 and 12.27 (each 1H, brs, NH); ms: (CI) m/z 234 (MH^+). *Anal.* Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.85; H, 4.81; N, 17.85.

6-(4-Chlorobenzyl)-1,3,5-triazine-2,4(1*H*, 3*H*)-dione (5n). This compound was obtained as a colorless powder, mp 273° dec; ir: 3124, 1755, 1672, 1602, 1587, 1493, 1425 cm^{-1}; ^{1}H nmr: δ 3.75 (2H, s, CH_2), 7.36 and 7.40 (each 2H, d, J=8.6 Hz, aromatic), 11.27 and 12.31 (each 1H, brs, NH); ms: (CI) m/z 238 (MH^+). *Anal.* Calcd. for $C_{10}H_8ClN_3O_2$: C, 50.54; H, 3.39; N, 17.68. Found: C, 50.61; H, 3.40; N, 17.33.

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