Retro-Ene Reactions in Heterocyclic Synthesis. IV [1]. A New Synthetic Method for 6-Hydroxypyrimidin-4(3*H*)-ones and 1,3,5-Triazine-2,4(1*H*,3*H*)-diones

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N-*t*-Butylbenzamidines **1** reacted with diphenyl phenylmalonate or diphenyl methylmalonate to give 6-hydroxypyrimidin-4(3*H*)-ones **4** or **5**. Amidines **1** on reaction with diphenyl imidodicarboxylate afforded 1,3,5-triazine-2,4(1*H*,3*H*)-diones **8**.

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Previously we reported on a new synthetic method for a variety of 2-amino and 2-hydroxypyridine derivatives *via* sterically assisted retro-ene reactions [2,3]. The present paper deals with an extension of this method to the synthesis of 6-hydroxypyrimidin-4(3*H*)-ones and 1,3,5-triazine-2,4(1*H*,3*H*)-diones.

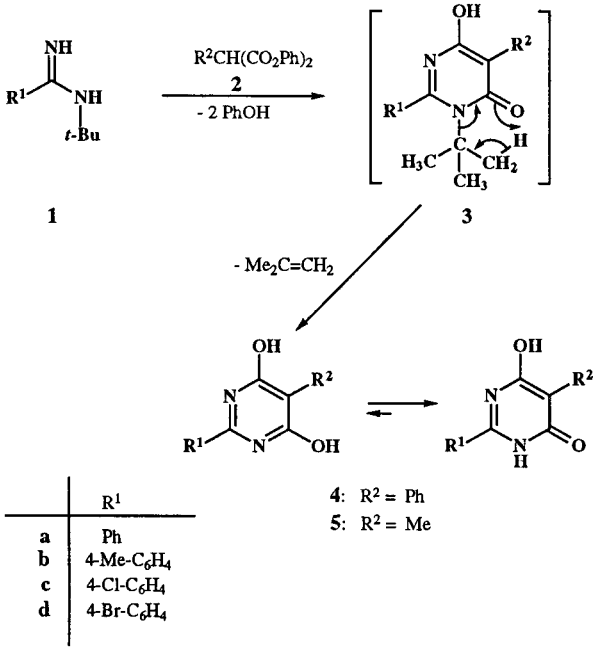
When a solution of *N*-*t*-butylbenzamidines **1** in diglyme was added dropwise to a stirred solution of diphenyl phenylmalonate (**2**, R^2 = Ph) or diphenyl methylmalonate (**2**, R^2 = Me) in diglyme and the mixture was heated at 80° or 120°, 6-hydroxypyrimidin-4(3*H*)-ones **4** or **5** were obtained *via* a retro-ene reaction (Scheme 1). The results obtained are summarized in Table 1. The low temperature (80-120°) required for this retro-ene reaction is noteworthy since the retro-ene reaction, in general, takes place at high temperature [4].

Table 1

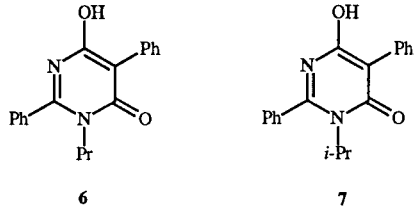
Preparation of Compounds **4**, **5** and **8**

Compound	Reaction Temperature °C	Reaction Time/hours	Yield %
4a	80	10	89
4b	80	10	84
4c	80	10	86
4d	80	10	88
5a	120	10	82
5b	120	10	82
5c	120	10	85
5d	120	10	80
8a	120	10	90
8b	130	5	93
8c	130	5	92
8d	130	5	94

Scheme 1

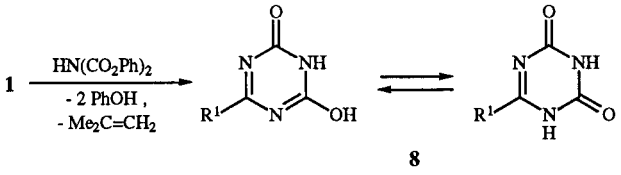


N-Propylbenzamidine and *N*-isopropylbenzamidine when heated with diphenyl phenylmalonate (**2**, R^2 = Ph) at 150° for 10 hours in diglyme gave 3-substituted 6-hydroxypyrimidin-4(3*H*)-ones **6** and **7** in 90 and 88% yield, respectively; the retro-ene reaction product **4a** could not be isolated. The steric strain between the *t*-butyl and R^1 groups in the intermediates **3** constitutes an important factor in causing the easy elimination of 2-methylpropene to take place.



Similarly, *N*-*t*-butylbenzamidines **1** on reaction with diphenyl imidodicarboxylate at 120-130° gave 1,3,5-triazine-2,4(1*H*,3*H*)-diones **8** [5] (Scheme 2) in high yields. The results obtained are summarized in Table 1.

Scheme 2



8

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded in potassium bromide pellets on a JEOL JIR-7000 spectrometer. The ^{1}H nmr data were obtained with a JEOL JNM-EX400 (400 MHz) spectrometer in deuteriodimethyl sulfoxide by using tetramethylsilane as an internal standard. Mass spectra were measured with a Shimadzu GCMS-QP1000 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-Butylbenzamidines **1**, *N*-propylbenzamidine and *N*-isopropylbenzamidine were prepared by the method of Cooper and Partridge [6]. Diphenyl phenylmalonate (**2**, R^2 = Ph) and diphenyl methylmalonate (**2**, R^2 = Me) were prepared according to the method of Ziegler and Junek [7]. Diphenyl imidodicarboxylate was obtained according to the procedure of Usui *et al.* [8].

6-Hydroxypyrimidin-4(3*H*)-ones **4** and **5**.

To a stirred solution of esters **2** (20.0 mmoles) in diglyme (20 ml) was added a solution of *N-t*-butylbenzamidines **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 filtrates *in vacuo* and washing the residual solid with ether (5 ml) gave an additional amount of product. All the products (**4** and **5**) obtained were of satisfactory purity as judged by ^{1}H nmr spectroscopy. Samples for analysis were recrystallized from dimethyl formamide.

6-Hydroxy-2,5-diphenylpyrimidin-4(3*H*)-one (**4a**).

This compound was obtained as a yellow powder, mp 401° dec; ir: 2677, 1608, 1581, 1518 cm^{-1}; ^{1}H nmr: δ 7.19-8.15 (10H, m, aromatic), 11.68 (2H, br s, OH and NH); ms: (CI), m/z 265 (MH^+).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.92; H, 4.66; N, 10.33.

6-Hydroxy-2-(4-methylphenyl)-5-phenylpyrimidin-4(3*H*)-one (**4b**).

This compound was obtained as a yellow powder, mp 404° dec; ir: 2686, 1608, 1581, 1514 cm^{-1}; ^{1}H nmr: δ 2.39 (3H, s, CH_3), 7.18-7.34 (5H, m, aromatic), 7.56 and 8.05 (each 2H, d, J = 8.3 Hz, aromatic), 11.64 (2H, br s, OH and NH); ms: (CI), m/z 279 (MH^+).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.31; H, 5.09; N, 9.87.

2-(4-Chlorophenyl)-6-hydroxy-5-phenylpyrimidin-4(3*H*)-one (**4c**).

This compound was obtained as yellow needles, mp 417° dec; ir: 2681, 1608, 1576, 1510 cm^{-1}; ^{1}H nmr: δ 7.20-7.56 (5H, m, aromatic), 7.59 and 8.16 (each 2H, d, J = 8.8 Hz, aromatic), 11.73 (2H, br s, OH and NH); ms: (CI), m/z 299 (MH^+).

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.40; H, 3.65; N, 9.16.

2-(4-Bromophenyl)-6-hydroxy-5-phenylpyrimidin-4(3*H*)-one (**4d**).

This compound was obtained as a yellow powder, mp 419° dec; ir: 2684, 1606, 1574, 1514 cm^{-1}; ^{1}H nmr: δ 7.20-7.55 (5H, m, aromatic), 7.73 and 8.08 (each 2H, d, J = 8.8 Hz, aromatic), 11.76 (2H, br s, OH and NH); ms: (CI), m/z 343 and 345 (MH^+).

Anal. Calcd. for $C_{16}H_{11}BrN_2O_2$: C, 56.00; H, 3.23; N, 8.16. Found: C, 56.01; H, 3.22; N, 7.95.

6-Hydroxy-5-methyl-2-phenylpyrimidin-4(3*H*)-one (**5a**).

This compound was obtained as pale yellow needles, mp 377° dec; ir: 2627, 1624, 1585, 1514 cm^{-1}; ^{1}H nmr: δ 1.84 (3H, s, CH_3), 7.47-7.54 and 8.08-8.10 (3H and 2H, m, aromatic), 11.41 (2H, br s, OH and NH); ms: (CI), m/z 203 (MH^+).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.50; H, 4.92; N, 13.84.

6-Hydroxy-5-methyl-2-(4-methylphenyl)pyrimidin-4(3*H*)-one (**5b**).

This compound was obtained as pale yellow needles, mp 382° dec; ir: 2661, 1616, 1579, 1510 cm^{-1}; ^{1}H nmr: δ 1.83 (3H, s, CH_3), 2.37 (3H, s, CH_3), 7.29 and 7.98 (each 2H, d, J = 8.3 Hz, aromatic), 11.31 (2H, br s, OH and NH); ms: (CI), m/z 217 (MH^+).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.57; H, 5.63; N, 12.74.

2-(4-Chlorophenyl)-6-hydroxy-5-methylpyrimidin-4(3*H*)-one (**5c**).

This compound was obtained as pale yellow needles, mp 412° dec; ir: 2621, 1618, 1576, 1497 cm^{-1}; ^{1}H nmr: δ 1.85 (3H, s, CH_3), 7.54 and 8.10 (each 2H, d, J = 8.8 Hz, aromatic), 11.41 (2H, br s, OH and NH); ms: (CI), m/z 237 (MH^+).

Anal. Calcd. for $C_{11}H_9ClN_2O_2$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.99; H, 3.79; N, 11.74.

2-(4-Bromophenyl)-6-hydroxy-5-methylpyrimidin-4(3*H*)-one (**5d**).

This compound was obtained as pale yellow needles, mp 413° dec; ir: 2617, 1618, 1572, 1500 cm^{-1}; ^{1}H nmr: δ 1.85 (3H, s, CH_3), 7.69 and 8.03 (each 2H, d, J = 8.8 Hz, aromatic), 11.43 (2H, br s, OH and NH); ms: (CI), m/z 281 and 283 (MH^+).

Anal. Calcd. for $C_{11}H_9BrN_2O_2$: C, 47.00; H, 3.23; N, 9.97. Found: C, 47.15; H, 3.24; N, 9.65.

6-Hydroxy-2,5-diphenyl-3-propylpyrimidin-4(3*H*)-one (**6**).

To a stirred solution of diphenyl phenylmalonate (**2**, R^2 = Ph) (6.65 g, 20.0 mmoles) in diglyme (20 ml) was added a solution of *N*-propylbenzamidine (3.24 g, 20.0 mmoles) in diglyme (20 ml) during 10 minutes. The mixture was heated with stirring at 150° for 10 hours. The reaction mixture was worked up in the same manner as described in the preparation of compounds **4** and **5** to give **6** (5.51 g, 90%) as pale yellow needles, mp 260-261° (from dimethylformamide); ir: 2677, 1659, 1618, 1529, 1443 cm^{-1}; ^{1}H nmr: δ 0.67 (3H, t, J = 7.6 Hz, CH_3), 1.52 (2H, sextet, J = 7.6 Hz, $CH_2CH_2CH_3$), 3.79 (2H, t, J = 7.6 Hz, $CH_2CH_2CH_3$), 7.18-7.62 (10H, m, aromatic), 11.28 (1H, br s, OH); ms: (CI), m/z 307 (MH^+).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.62; H, 5.90; N, 9.01.

6-Hydroxy-3-isopropyl-2,5-diphenylpyrimidin-4(3*H*)-one (**7**).

From diphenyl phenylmalonate (**2**, R^2 = Ph) (6.65 g, 20.0 mmoles) and *N*-isopropylbenzamidine (3.24 g, 20.0 mmoles) compound **7** was obtained by the same procedure as described above as pale yellow prisms (5.40 g, 88%), mp 278-278.5° (from dimethyl formamide); ir: 2630, 1670, 1620, 1522, 1497, 1423 cm^{-1}; ^1H nmr: δ 1.47 (6H, d, J = 6.8 Hz, 2 CH_3), 4.24 (1H, septet, J = 6.8 Hz, CH), 7.17-7.59 (10H, m, aromatic), 11.18 (1H, br s, OH); ms: (CI), m/z 307 (MH^+).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.32; H, 5.92; N, 8.99.

1,3,5-Triazine-2,4(1*H*,3*H*)-diones **8**.

To a stirred solution of diphenyl imidodicarboxylate (20.0 mmoles) in diglyme (20 ml) was added a solution of *N*-*t*-butylbenzamidines **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 monoglyme (10 ml). Evaporation of the combined filtrates *in vacuo* and washing the residual solid with monoglyme (5 ml) gave an additional amount of product. All the products **8** obtained were of satisfactory purity as judged by ^1H nmr spectroscopy. Samples for analysis were recrystallized from dimethyl formamide.

6-Phenyl-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**8a**).

This compound was obtained as colorless prisms, mp 290° dec (reference [9], mp 286-288°); ir: 2816, 1728, 1676, 1605, 1566, 1483, 1404 cm^{-1}; ^1H nmr: δ 7.52-8.10 (5H, m, aromatic), 11.13 and 12.12 (each 1H, br s, OH or NH); ms: (CI), m/z 190 (MH^+).

6-(4-Methylphenyl)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**8b**).

This compound was obtained as a colorless powder, mp 310.5° dec; ir: 2800, 1730, 1684, 1601, 1558, 1485, 1416 cm^{-1}; ^1H nmr: δ 2.39 (3H, s, CH_3), 7.35 and 8.01 (each 2H, d, J = 8.3 Hz, aromatic), 11.07 and 12.05 (each 1H, br s, OH or NH); ms: (CI), m/z 204 (MH^+).

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.40; H, 4.33; N, 20.75.

6-(4-Chlorophenyl)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**8c**).

This compound was obtained as a colorless powder, mp 318° dec; ir: 2818, 1743, 1676, 1593, 1561, 1477, 1414 cm^{-1}; ^1H nmr: δ 7.60 and 8.10 (each 2H, d, J = 8.8 Hz, aromatic), 11.15 and 12.02 (each 1H, br s, OH or NH); ms: (CI), m/z 224 (MH^+).

Anal. Calcd. for $C_9H_6ClN_3O_2$: C, 48.34; H, 2.70; N, 18.79. Found: C, 48.27; H, 2.46; N, 18.83.

6-(4-Bromophenyl)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**8d**).

This compound was obtained as colorless needles, mp 325.5° dec; ir: 2814, 1741, 1674, 1595, 1558, 1473, 1417 cm^{-1}; ^1H nmr: δ 7.74 and 8.02 (each 2H, d, J = 8.8 Hz, aromatic), 11.16 and 12.20 (each 1H, br s, OH or NH); ms: (CI), m/z 268 and 270 (MH^+).

Anal. Calcd. for $C_9H_6BrN_3O_2$: C, 40.33; H, 2.26; N, 15.68. Found: C, 40.37; H, 2.14; N, 15.83.

REFERENCES AND NOTES

[1] For Part III see: K. Ito and S. Miyajima, *J. Heterocyclic Chem.*, **34**, 501 (1997).

[2] K. Ito, S. Yokokura and S. Miyajima, *J. Heterocyclic Chem.*, **26**, 773 (1989).

[3] K. Ito and S. Miyajima, *J. Heterocyclic Chem.*, **29**, 1037 (1992).

[4] For reviews of the retro-ene reaction, see: H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969); J.-L. Ripoll and Y. Vallée, *Synthesis*, 659 (1993).

[5] For the tautomerism of 1,3,5-triazine-2,4(1*H*,3*H*)-dione, see: D. Bartholomew, in Comprehensive Heterocyclic Chemistry II, Vol **6**, A. J. Boulton, ed, Elsevier Science, Oxford, 1996, p 590.

[6] F. C. Cooper and M. W. Partridge, in Organic Syntheses, Coll Vol **4**, A. H. Blatt, ed, John Wiley & Sons, New York, NY, 1963, p 769.

[7] E. Ziegler and H. Junek, *Monatsh. Chem.*, **86**, 29 (1955).

[8] H. Usui, Y. Watanabe and M. Kaneko, *J. Heterocyclic Chem.*, **30**, 551 (1993).

[9] M. N. Basyouni and A.-M. El-Khamry, *Bull. Chem. Soc. Japan*, **52**, 3728 (1979).