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Novel and Chemoselective Dehydrogenation of 3,4-Dihydropyrimidin-2(1*H*)-ones with 1,4-Bis(triphenylphosphonium)-2-butene Peroxodisulfate

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3,4-Dihydropyrimidin-2(1*H*)-ones were efficiently converted into the corresponding pyrimidin-2(1*H*)-ones in high yields within a short period of time on treatment with aqueous acetonitrile using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate. Chemoselective oxidation of 3,4-dihydropyrimidin in the presence of other oxidizable functional groups was also achieved by this reagent.

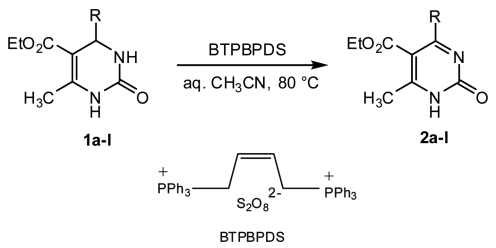
Key Words : Dehydrogenation, Pyrimidin-2(1*H*)-ones, 3,4-Dihydropyrimidin-2(1*H*)-ones, 1,4-Bis(triphenylphosphonium)-2-butene peroxodisulfate

Introduction

The oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) to pyrimidin-2(1*H*)-ones is biologically and pharmaceutically very important.[1] 3,4-dihydropyrimidin-2(1*H*)-ones can be easily prepared from ethyl acetoacetate, aromatic aldehyde and urea.[2] Therefore, dehydrogenation of DHPMs by an oxidizing agent should provide an efficient method for the preparation of pyrimidin derivatives. Several reagents such as $NaNO_2$/AcOH,[3] CAN/AcOH,[4] $KMnO_4$/clay,[3] $Co(NO_3)_2{\cdot}6H_2O$/$K_2S_2O_8$,[5] $FeCl_3$[6] have been previously reported for this purpose. These reagents suffer from limitations such as low yields of the products, long reaction times, the use of large excess of the reagents, and harsh reaction conditions. Therefore, the discovery of a novel, mild and efficient method using an inexpensive reagent for high-yielding oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones to their corresponding pyrimidines is of general interest.

Peroxodisulfate ion is an excellent and versatile oxidant; used mostly for the oxidation of compounds in aqueous solution.[7] In spite of the great convenience of using $K_2S_2O_8$, $Na_2S_2O_8$, $(NH_4)_2S_2O_8$ and relatively high oxidation potential, many oxidations by peroxodisulfate do not proceed at a convenient rate, so, recently; the modification of $K_2S_2O_8$ has attracted a great deal of attention.[8]

Recently 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate (BTPBPDS), an inexpensive and environmentally safe oxidation reagent, has been used for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles,[9] iodination of aromatic compounds,[10] synthesis of phenacyl thiocyanates and phenacyl azides[11] and synthesis of β-nitrato alcohols.[12] Herein, we wish to report oxidation of various types of 3,4-dihydropyrimidin-2(1*H*)-ones with BTPBPDS as an efficient reagent (Scheme 1).



Scheme 1. Oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones using BTPBPDS.

Our goals in undertaking this work were: (a) to achieve rapid reaction rates, higher yields, and milder reaction conditions; (b) to overcome the drawbacks of the reported methods; (c) to develop a high-yielding synthesis of pyrimidines using a cheap reagent.

Experimental

All products were characterized by comparison of their physical data, IR, ^{1}H NMR, and ^{13}C NMR spectra with authentic samples. ^{1}H NMR and ^{13}C NMR spectra were taken on a 400 MHz Brucker Spectrometer. IR spectra were recorded on Bomem MB-Series 1998 FT-IR spectrometer. 1,4-Bis(triphenylphosphonium)-2-butene peroxodisulfate was prepared as described in our previous papers[12] and other chemicals were purchased from the Merck Chemical Company, Darmstadt, Germany. The purity determination of the products and reaction monitoring were accomplished by TLC on polygram SILG/UV 254 plates.

General Procedure for the Oxidation of 3,4-Dihydropyrimidin-2(1*H*)-ones. To a solution of 3,4-dihydropyrimidin-2(1*H*)-one (1 mmol) in acetonitrile and water (10:2 mL) in a 50 mL round-bottomed ask equipped with a condenser and a magnetic stirrer, 1,4-bis(triphenylphosphonium)-2-butene peroxo disulfate (1 mmol) was added in small portions. The reaction mixture was refluxed for the appropriate time indicated in Table 1. The progress of the reaction was monitored by TLC. Upon completion of the reaction, it was cooled to room temperature and filtered. Water (15 mL) was added and extracted with chloroform (3 × 15 mL). The combined organic layers solution was dried over $MgSO_4$.

The solvent was concentrated in vacuo; the resulting product was directly charged on a small silica gel column and eluted with a mixture of diethyl ether and *n*-hexane (1:4) to afford the pure product.

Spectral Data of Pyrimidin-2(1*H*)-ones are Listed Below.

Ethyl 6-Methyl-4-phenylpyrimidin-2(1*H*)-one-5-carboxylate (2a): mp 132-133 °C.[13] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.78 (t, *J* = 7.08 Hz, 3H), 2.49 (s, 3H), 3.88 (q, *J* = 7.08 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.45-7.48 (m, 3H), 11.71 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.6 (CH_3), 61.0 (CH_2), 108.5 (C), 128.01 (CH), 128.72 (CH), 130.7 (CH), 138.1 (C), 158.5 (C), 162.5 (C), 164.7 (C), 165.9 (C).

Ethyl 6-Methyl-4-(4-chlorophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2b): mp 184-185 °C.[14] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.05 Hz, 3H), 2.58 (s, 3H), 3.96 (q, *J* = 7.05 Hz, 2H), 7.42 (d, *J* = 8.33 Hz, 2H), 7.59 (d, *J* = 8.33 Hz, 2H), 12.01 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 19.1 (CH_3), 61.2 (CH_2), 108.9 (C), 127.8 (CH), 128.9 (CH), 135.9 (C), 137.2 (C), 158.7 (C), 162.8 (C), 165.2 (C), 166.50 (C).

Ethyl 6-Methyl-4-(4-methylphenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2c): mp 139-140 °C.[13] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.93 Hz, 3H), 2.46 (s, 3H), 2.52 (s, 3H), 3.98 (q, *J* = 6.93 Hz, 2H), 7.14 (d, *J* = 7.22 Hz, 2H), 7.55 (d, *J* = 7.11 Hz, 2H), 11.87 (brd s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 19.0 (CH_3), 21.3 (CH_3), 61.5 (CH_2), 108.2 (C), 127.1 (CH), 128.9 (CH), 129.2 (C), 140.8 (C), 158.2 (C), 161.9 (C), 164.4 (C), 166.8 (C).

Ethyl 6-Methyl-4-(4-methoxyylphenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2d): mp 152 °C.[13] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J*=6.71 Hz, 3H), 2.48 (s, 3H), 2.61 (s, 3H), 3.85 (q, *J* = 6.80 Hz, 2H), 6.87 (d, *J* = 8.62 Hz, 2H), 7.12 (d, *J* = 8.72 Hz, 2H), 10.17 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 19.5 (CH_3), 55.2 (CH_3), 61.5 (CH_2), 108.2 (C), 110.8 (CH), 124.01 (CH), 127.3 (C), 158.2 (C), 159.1 (C), 162.5 (C), 164.5 (C), 167.1 (C).

Ethyl 6-Methyl-4-(4-nitrophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2e): mp 154-155 °C.[13] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.03 Hz, 3H), 2.68 (s, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 7.57 (d, *J* = 8.12 Hz, 2H), 7.64 (d, *J* = 8.12 Hz, 2H), 12.89 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.7 (CH_3), 61.3 (CH_2), 108.1 (C), 125.0 (CH), 127.6 (CH), 143.1 (C), 149.2 (C), 158.4 (C), 162.6 (C), 164.7 (C), 166.1 (C).

Ethyl 6-Methyl-4-(3-nitrophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2f): mp 167-168 °C.[14] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.05 Hz, 3H), 2.64 (s, 3H), 4.01 (q, *J* = 7.05 Hz, 2H), 7.84 (m, 2H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.35 (s, 1H), 12.79 (brd s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 18.1 (CH_3), 61.0 (CH_2), 107.8 (C), 122.3 (CH), 125.4 (CH), 130.72 (CH), 131.9 (C), 134.2(CH), 149.1 (C), 158.7 (C), 163.0 (C), 164.7 (C), 169.1 (C).

Ethyl 6-Methyl-4-(3-bromophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2g): mp 107-108 °C.[14] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.05 Hz, 3H), 2.58 (s, 3H), 3.99 (q, *J* = 7.23 Hz, 2H), 7.37 (t, *J* = 7.81 Hz, 1H), 7.59-7.67 (m, 3H), 12.03 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.4 (CH_3), 61.1 (CH_2), 107.5 (C), 124.1 (C), 126.9 (CH), 130.2 (CH), 132.3 (CH), 133.2 (CH), 134.6 (C), 158.8 (C), 162.8 (C), 164.7 (C), 166.1 (C).

Ethyl 6-Methyl-4-(2,4-dichlorophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2h): mp 197-198 °C. IR (KBr) ν 3220, 2978, 2924, 1715, 1650, 1590, 1444, 1390, 1287, 1220, 1078, 860, 775 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.09 Hz, 3H), 2.59 (s, 3H), 4.00 (q, *J* = 7.09 Hz, 2H), 7.35 (d, *J* = 7.87 Hz, 1H), 7.49 (d, *J* = 7.95 Hz, 1H), 7.59 (s, 1H), 12.11 (brd s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.2 (CH_3), 61.0 (CH_2), 108.7 (C), 127.9 (CH), 130.1 (CH), 131.5 (CH), 132.9 (C), 134.7 (C), 136.9 (C), 159.2 (C), 163.2 (C), 164.7 (C), 169.1 (C).

Ethyl 6-Methyl-4-(2-chlorophenyl)pyrimidin-2(1*H*)-one-5-carboxylate (2i): mp 181-183 °C.[13] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.75 (t, *J* = 6.80 Hz, 3H), 2.50 (s, 3H), 3.82 (q, *J* = 6.80 Hz, 2H), 7.37-7.39 (m, 4H), 11.61 (brd s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.6 (CH_3), 61.0 (CH_2), 109.0 (C), 126.9 (CH), 128.8 (CH), 129.7 (CH), 130.7 (CH), 132.1 (C), 138.7 (C), 159.7 (C), 162.5 (C), 164.6 (C), 169.8 (C).

Ethyl 6-Methyl-4-(2-furyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2j): mp 99-101 °C. IR (KBr) ν 3050, 2965, 2875, 1702, 1600, 1510, 1420, 1380, 1280, 1100, 910, 850, 625 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.80 Hz, 3H), 2.58 (s, 3H), 3.90 (q, *J* = 6.80 Hz, 2H), 6.71 (t, *J* = 3.83 Hz, 1H), 7.33 (d, *J* = 2.02 Hz, 1H), 7.48 (d, *J* = 3.71 Hz, 1H), 11.33 (brd s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 17.3 (CH_3), 61.1 (CH_2), 107.1 (C), 112.6 (CH), 114.2 (CH), 142.4 (CH), 144.5 (C), 158.5 (C), 161.3 (C), 162.0 (C), 163.1 (C).

Ethyl 6-Methyl-4-propyl-pyrimidin-2(1*H*)-one-5-carboxylate (2k): mp 106-109 °C. IR (KBr) ν 3380, 3150, 1695, 1640, 1570, 1452, 1362, 1255, 1131, 998, 824, 789 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.78 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.05 Hz, 3H), 1.35 (m, 2H), 2.38 (t, *J* = 6.03 Hz, 2H), 2.51 (s, 3H), 3.80 (q, *J* = 7.05 Hz, 2H), 11.81 (brd s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.1 (CH_3), 13.8 (CH_3), 17.4 (CH_3), 22.45 (CH_2), 28.63 (CH_2), 60.1 (CH_2), 109.5 (C), 158.9 (C), 162.5 (C), 163.8 (C), 171.1 (C).

Ethyl 6-Methyl-4-cyclohexyl-pyrimidin-2(1*H*)-one-5-carboxylate (2l): mp 99-101 °C. IR (KBr) ν 3290, 3040, 1690, 1645, 1510, 1413, 1338, 1242, 1029, 725, 695, 635 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.43 Hz, 3H), 1.11-1.17 (m, 2H), 1.42-1.47 (m, 4H), 1.68-1.75 (m, 4H), 2.49 (s, 3H), 3.82 (q, *J* = 7.45 Hz, 2H), 10.87 (brd s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.5 (CH_3), 17.5 (CH_3), 25.4 (CH_2), 26.1 (CH_2), 29.8 (CH_2), 30.7 (CH), 61.1 (CH_2), 109.3 (C), 158.9 (C), 162.4 (C), 164.1 (C), 177.3 (C).

Results and Discussion

1,4-Bis(triphenylphosphonium)-2-butene peroxodisulfate can be readily prepared by adding an aqueous solution of potassium peroxodisulfate to a solution of 1,4-bis(triphenylphosphonium)-2-butene dichloride in water. This white solid is very stable and can be stored for months without losing its

Table 1. Oxidation of 3,4-dihydropyrimidines with BTPBPDS in CH_3CN under reflux condition

Product	R	Time (min)	Yield[a] (%)
2a	C_6H_5	80	82
2b	4-Cl–C_6H_4	85	90
2c	4-Me–C_6H_4	65	91
2d	4-OMe–C_6H_4	50	87
2e	4-NO_2–C_6H_4	90	79
2f	3- NO_2–C_6H_4	110	85
2g	3-Br–C_6H_4	85	90
2h	2,4-Cl_2–C_6H_3	90	82
2i	2-Cl–C_6H_4	110	81
2j	2-Furyl	85	90
2k	*n*-C_3H_7	75	82
2l	C_6H_{11}	80	88

[a]Isolated yield

activity. It is soluble in acetonitrile, methanol, dichloromethane, chloroform and ethyl acetate and slightly soluble in CCl_4 and diethyl ether. To gain some preliminary information on this synthetically useful reaction, we studied the influence of different factors: solvent, molar ratio and temperature on the reaction kinetics. Thus, the effect of various solvents on the reaction rate and yield were investigated.

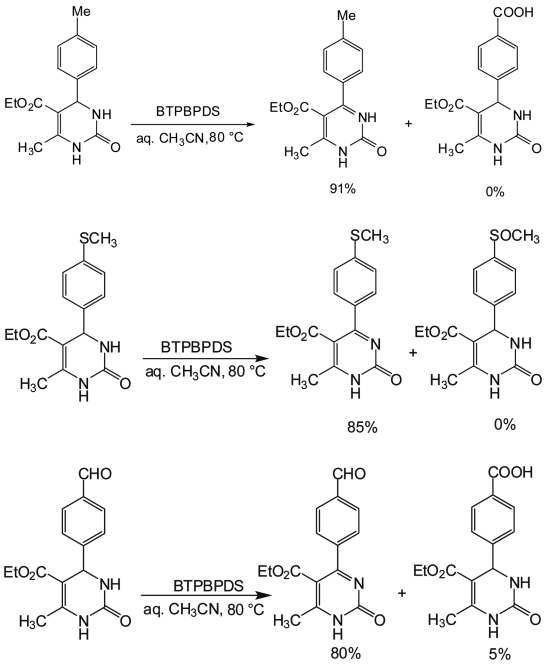
The experimental results showed that acetonitrile was the best choice for our procedure. Also our observations revealed that the molar ratio of 1.0:1.0 for DHPMs/BTPBPDS and reflux condition were the most effective, giving short reaction times and clean products. It is noteworthy that the presence of water was necessary for the reaction since the reaction of **1a** in dry acetonitrile did not result in the occurrence of any reaction. The reaction mixture at room temperature up to 48 h gave no appreciable amount of product, whereas total oxidation of **1a** was observed after 80 min when refluxed.

As shown in Table 1, different types of DHPMs are oxidized to their corresponding products in high to excellent yields (entries **1a-l**). Some of the reported reagents such as MnO_2,[3] $RuCl_3/O_2$ in AcOH,[15] PCC,[3] DDQ,[3] chloranil,[3] Br_2,[16] Sulfur[17] and Pd/C[3] were not effective for dehydrogenation of DHPMs. Thus, effcient oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones to their pyrimidin-2(1*H*)-ones by BTPBPDS/CH_3CN system is an interesting feature of the presented method. Aliphatic substituents such as propyl and cyclohexyl at C-4 of the DHPMs (entries 1k and 1l) also gave clean oxidative dehydrogenation without the formation of any concomitant dealkylation product.

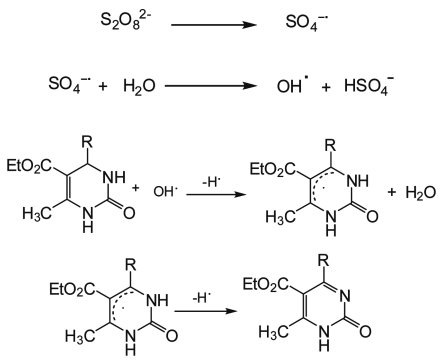
In order to establish the general applicability of the method, we have performed several competitive oxidation reactions, results of which are shown in Scheme 2. As can be seen, interesting chemoselective oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones in the presence of other oxidizable functional groups such as sulfide, alkyl, and aldehydes, is achieved using this reagent system. To the best of our knowledge, such selectivities have not been reported previously in oxidation of dihydropyrimidines.

DHPMs with aryl groups containing either electron-withdrawing or electron-releasing substituent showed no difference and afforded the corresponding products in high yields. A mechanistic rationalization of this oxidation process may lead to pyrimidinone presented as follows. Oxidation of the water by sulfate anion radical would lead to the hydroxyl radical. Conceivably addition of the latter to the DHPM will result in the dihydropyrimidonyl radical. This can eliminate the other hydrogen atom to form the corresponding pyrimidinone. The presence of enough water CH_3CN/H_2O (5:2) is necessary for the reaction, since the reaction would not take place in dry acetonitrile and when the reactions were carried out in CH_3CN/H_2O (5:1), they were not complete. The reason for inefficient reaction in CH_3CN/H_2O (5:1) may be due to the formation of lower hydroxyl radical.

A mechanistic rationalization of this oxidation process may lead to pyrimidinone presented as follows (Scheme 3).



Scheme 2. Chemo selective oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones in the presence of other oxidizable functional groups.



Scheme 3. Mechanistic outlines for the formation of pyrimidin-2(1*H*)-ones.

Conclusion

In summary, the advantage of this method is simplicity, mild reaction conditions, high yields of the products accompanied with chemoselectivity, the use of lower molar ratio of DHPMs:oxidant (1:1) compared with DHPMs/CAN (1:5) in AcOH[4] or with DHPMs/CAN/$NaHCO_3$ (1:3:5)[4] in acetone and with DHPMs/$Co(NO_3)_2{\cdot}6H_2O$/$k_2S_2O_8$ (1:5:2.5).[5]

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