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Rapid dehydrogenation of 3,4-dihydropyrimidin-2(1H)-ones using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate and microwave heating

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Efficient oxidative dehydrogenation of 3,4-dihydropyrimidin-2(1H)-ones to pyrimidin-2(1H)-ones was achieved using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate as an oxidant under microwave irradiation. Chemoselective oxidation of 3,4-dihydropyrimidine in the presence of other oxidizable functional groups such as sulfide, alkyl, aldehyde was also achieved by this reagent.

Keywords: 3,4-dihydropyrimidin-2(1H)-ones; pyrimidin-2(1H)-ones; 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate; microwave irradiation; dehydrogenation.

INTRODUCTION

Microwave radiation provides an alternative to conventional heating, as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. The use of microwave irradiation has introduced several new concepts in chemistry. Absorption and transmission of the energy is completely different from the conventional mode of heating. The microwave technology has been applied to a number of useful research and development processes such as polymer technology, organic synthesis, application to waste treatment, drug release/targeting, ceramic and alkane decomposition [1-6] .

3,4-dihydropyrimidin-2(1H)-ones (DHPMs) are a class of heterocyclic compounds which have a wide range of biological activities in medicinal chemistry including antifungal [7], antiviral [8], anti-inflammatory [9], and antioxidative properties [10]. These compounds can be easily prepared from ethyl acetoacetate, aromatic aldehyde and urea [11]. Therefore, dehydrogenation of DHPMs by an oxidizing agent should provide an efficient method for the preparation of pyrimidine derivatives.

In this paper, we describe an eco-friendly new method that utilizes 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate as an efficient reagent for the oxidation of various types of 3,4-dihydropyrimidin-2(1H)-ones under microwave irradiation conditions.

Peroxodisulfate ion is an excellent and versatile oxidant used mostly for the oxidation of compounds in aqueous solution [12]. In spite of the great convenience of using $K_2S_2O_8$, $Na_2S_2O_8$ or $(NH_4)_2S_2O_8$ and their relatively high oxidation potential, many oxidations by peroxodisulfate do not proceed at a convenient rate. The decomposition of the peroxodisulfate ion requires strong mineral acids and heavy metal ions as catalysts, as well as protic and polar solvents; so the modification of $K_2S_2O_8$, $Na_2S_2O_8$ or $(NH_4)_2S_2O_8$ has attracted a great deal of attention [13].

EXPERIMENTAL

All products are known and were identified by comparison of their physical data, ^{1}H NMR and ^{13}C NMR spectra with those of authentic samples [14–16]. ^{1}H NMR and ^{13}C NMR spectra were taken on a 400 MHz Bruker spectrometer. The microwave reactions were carried out in a Milestone MW apparatus model MicroSynth (2500 W) equipped with a condenser. 1,4-Bis(triphenylphosphonium)-2-butene peroxodisulfate (BTPBPDS) was prepared as described in our previous paper [13] and other chemicals were purchased from Merck, 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(1H)-ones

A mixture of 3,4- dihydropyrimidin-2(1H)-one (DHPMs) (1.0 mmol), and 1,4-bis (triphenylphosphonium)-2-butene peroxodisulfate (1 mmol) in acetonitrile and water (4:1,5 ml) was magnetically stirred and heated at 140℃ by microwave radiation under reflux conditions for the time shown in Table 1. After completion of the

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reaction, cold water (5 ml) was added and the mixture was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$. The solvent was concentrated *in vacuo*; the resulting product was recrystallized from n-hexane/ethyl acetate to give the desired product (Table 1).

Table 1. Oxidation of 3,4-dihydropyrimidines with BTPBPDS in CH_3CN under microwave irradiation

Product	R	Time (Sec)	Yield [a] (%)
2a	C_6H_5	120	87
2b	4-Cl–C_6H_4	120	92
2c	4-Me–C_6H_4	90	88
2d	4-OMe–C_6H_4	60	85
2e	4-NO_2–C_6H_4	150	80
2f	3- NO_2–C_6H_4	190	88
2g	3-Br–C_6H_4	120	88
2h	2,4-Cl_2–C_6H_3	150	86
2i	2-Cl–C_6H_4	180	85
2j	2-Furyl	120	92
2k	n-C_3H_7	90	82
2l	C_6H_{11}	120	87

[a] Isolated yield

Spectral data of pyrimidin-2(1H)-ones

***Ethyl-6-methyl-4-phenylpyrimidin-2(1H)-one-5-carboxylate (2a)*:** M.p.: 132-133°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.78 (t, 3H), 2.49 (s, 3H), 3.88 (q, 2H), 7.35 (t, 2H), 7.45-7.48 (m, 3H), 11.71 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2b)*:** M.p.: 184-185 °C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.89 (t, 3H), 2.58 (s, 3H), 3.96 (q, 2H), 7.42 (d, 2H), 7.59 (d, 2H), 12.01 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2c)*:** M.p.: 139-140 °C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.84 (t, 3H), 2.46 (s, 3H), 2.52 (s, 3H), 3.98 (q, 2H), 7.14 (d, 2H), 7.55 (d, 2H), 11.87 (brd s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2d)*:** M.p.: 152°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.82 (t, 3H), 2.48 (s, 3H), 2.61 (s, 3H), 3.85 (q, 2H), 6.87 (d, 2H), 7.12 (d, 2H), 10.17 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate(2e)*:** Mp: 154-155°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ=1.05 (t, 3H), 2.68 (s, 3H), 4.15 (q, 2H), 7.57 (d, 2H), 7.64 (d, 2H), 12.89 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2f)*:** M.p.: 167-168°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 1.01 (t, 3H), 2.64 (s, 3H), 4.01 (q, 2H), 7.84 (m, 2H), 8.21 (d, 1H), 8.35 (s, 1H), 12.79 (brd s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2g)*:** M.p.: 107-108°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.93 (t, 3H), 2.58 (s, 3H), 3.99 (q, 2H), 7.37 (t, 1H), 7.59-7.67 (m, 3H), 12.03 (s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2h)*:** M.p.: 197-198°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.95 (t, 3H), 2.59 (s, 3H), 4.00 (q, 2H), 7.35 (d, 1H), 7.49 (d, 1H), 7.59 (s, 1H), 12.11 (brd s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2i)*:** M.p.: 181-183°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.75 (t, 3H), 2.50 (s, 3H), 3.82 (q, 2H), 7.37-7.39 (m, 4H), 11.61 (brd s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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(1H)-one-5-carboxylate (2j)*:** M.p.: 99-101°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.85 (t, 3H), 2.58 (s, 3H), 3.90 (q, 2H),6.71 (t, 1H), 7.33 (d, 1H), 7.48 (d, 1H), 11.33 (brd s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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).

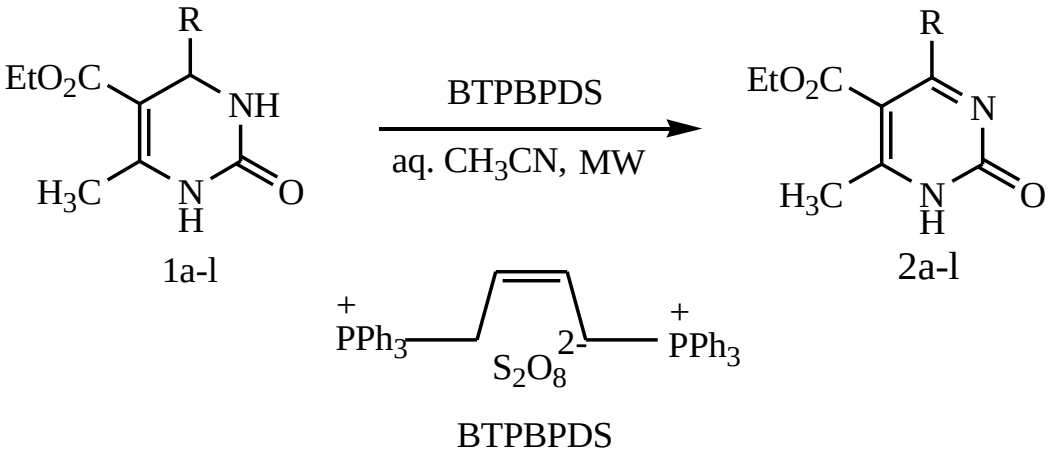
***Ethyl-6-methyl-4-propyl-pyrimidin-2(1H)-one-5-carboxylate (2k)*:** M.p.: 106-109°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.78 (t, 3H), 0.87 (t, 3H), 1.35 (m, 2H), 2.38 (t, 2H), 2.51 (s, 3H), 3.80 (q, 2H), 11.81 (brd s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): δ=13.1 (CH_3), 13.8 (CH_3), 17.4 (CH_3), 22.45(CH_2), 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(1H)-one-5-carboxylate (2l)*:** M.p.: 99-101°C. ^{1}H-NMR (400MHz, $CDCl_3$): δ= 0.79 (t, 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, 2H), 10.87 (brd s, 1H). ^{13}C-NMR (100MHz, $CDCl_3$): 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).

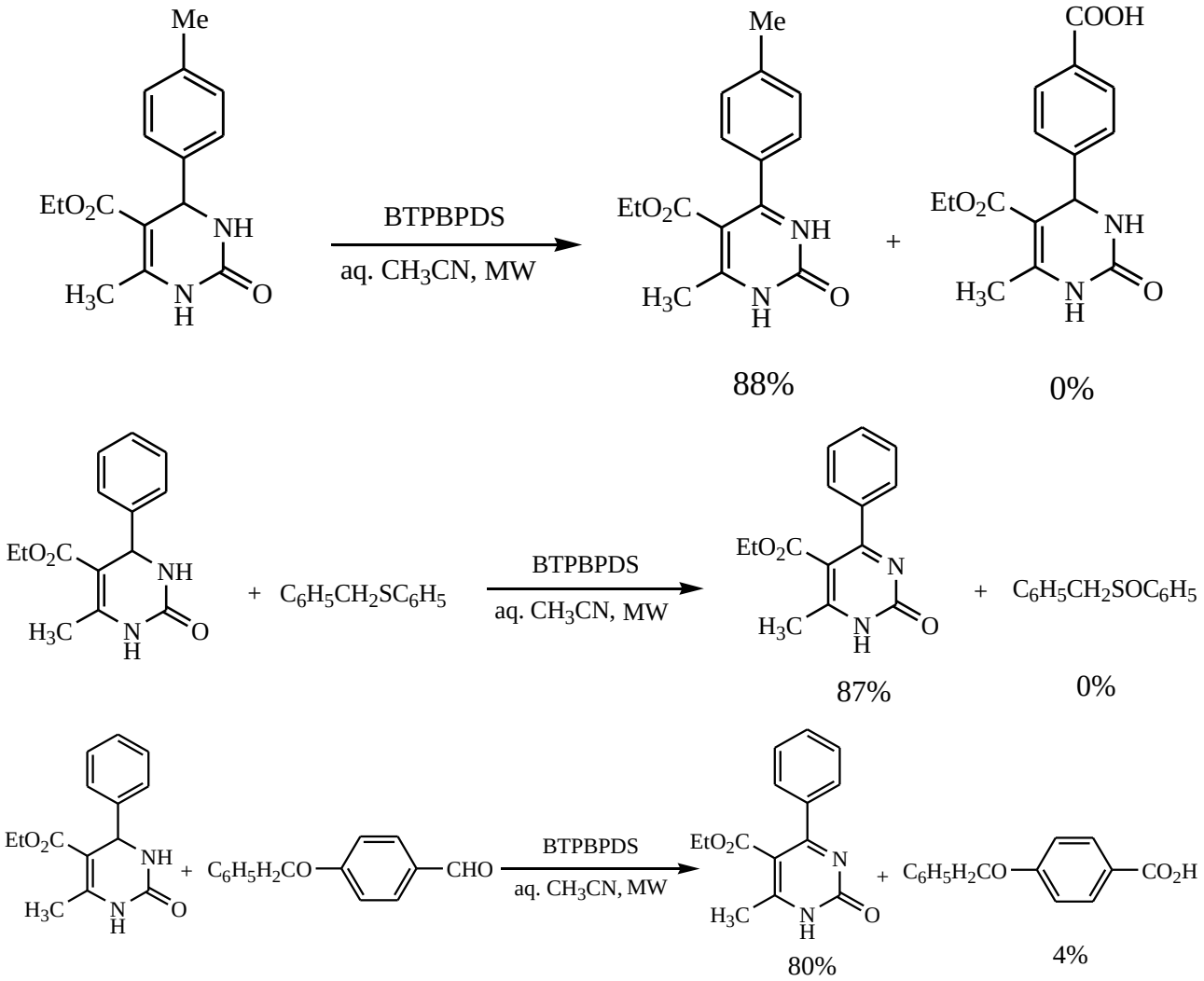
RESULTS AND DISCUSSION

1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate (BTPBPDS) was readily prepared by adding an aqueous solution of potassium peroxodisulfate to a solution of 1,4-bis(triphenylphosphonium)-2-butene dichloride in water. It is a very stable white solid which can be stored for months without losing its activity. It is soluble in acetonitrile, methanol, dichloromethane, chloroform and ethyl acetate and slightly soluble in CCl_4 and diethyl ether.

In order to explore the availability of 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate as an oxidant under microwave irradiation, oxidation of ethyl-6-methyl-4-phenylpyrimidin-2(1H)-one-5-carboxylate (1a) was selected as a model reaction. The optimal reaction conditions including reactant ratio, reaction time, kind of solvent and microwave power were investigated. It was found that at a ratio of DHPMs to BTPBPDS of 1:1, solvent acetonitrile and microwave power of 400 W (determined by the power adjustor of the microwave oven), the reaction gave the highest yield within 120 sec. It is noteworthy that the presence of water was necessary for the reaction since no reaction of 1a in dry acetonitrile took place. Using similar conditions, a series of 3,4-dihydropyrimidin-2(1H)-ones (1a-l) were synthesized in high yield (Scheme 1). The protocol is suitable for dehydrogenation of aryl, alkyl and heterocyclic substituted DHPMs. Various aryl substituted pyrimidin-2(1H)-ones could be easily synthesized by this method. Different substituents (4-MeO, 4-Me, 4-NO_2, 4-Cl, 3-NO_2, 3-Br, 2-Cl and 2,4-Cl_2) on the aryl rings had no significant effect on the reaction conditions and the reaction yield. Alkyl groups, such as propyl and cyclohexyl substituted pyrimidines could also be readily prepared by this route (1k, 1l).



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



Scheme 2. Chemoselective oxidation of 3,4-dihydropyrimidin-2(1H)-ones in the presence of BTPBPDS

In addition, ethyl 4-(2-furyl)-6-methyl-pyrimidin-2(1H)-one-5-carboxylate (2j) could also be synthesized by this approach (1j). In order to establish the general applicability of the method, we have performed several competitive oxidation reactions, the results of which are shown in Scheme 2. As can be seen, interesting chemoselective oxidation of 3,4-dihydropyrimidin-2(1H)-ones in the presence of other oxidizable functional groups such as sulfide, alkyl, and aldehyde groups, is achieved using this reagent system. To the best of our knowledge, such selectivities have not been reported previously in oxidation of dihydropyrimidines.

The dehydrogenation mechanism may involve oxidation of the water by sulfate anion radicals to form hydroxyl radicals, which are further converted by hydrogen abstraction from the 4-position to form dihydropyrimidonyl radicals. This can eliminate the other hydrogen atom to form the corresponding pyrimidinone.

CONCLUSION

In conclusion, this method provides an excellent approach for the safe, rapid, inexpensive and simple synthesis of medicinally important pyrimidin-2(1H)-ones in a single step.

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БЪРЗО ДЕХИДРОГЕНИРАНЕ НА 3,4-ДИХИДРОПИРИМИДИН-2(1*H*)-ОНИ, ИЗПОЛЗВАЙКИ 1,4- БИС-(ТРИФЕНИЛФОСФОНИЕВ)-2-БУТЕН ПЕРОКСОСУЛФАТ И МИКРОВЪЛНОВО НАГРЯВАНЕ

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(Резюме)

Постигнато е ефективно окислително дехидрогениране на 3,4-дихидропиримидин-2(1*H*)-они с използването на 1,4- бис-(трифенилфосфониев)-2-бутен пероксосулфат като окислител при микровълново нагряване. Постигнато е и селективно окисление в присъствие на други окисляеми функционални групи, като сулфиди, алдехидни и алкилови с този реагент.