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Synthesis of Furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones From Alcohols Using T3P/DMSO

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T3P/DMSO is shown to be an effective and mild reagent for the one-pot synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones from a variety of alcohols. Alcohols are oxidized *in situ* to aldehydes under mild conditions, which undergo a three-component reaction with *N,N'*-dimethylbarbituric acid and various isocyanides to afford furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones in good yields.

Keywords: Furo[2,3-*d*]pyrimidine, T3P/DMSO, Oxidization, Isocyanide

INTRODUCTION

Fused pyrimidine compounds as furo[2,3-*d*]pyrimidine are an important class of heterocyclic compounds that exhibit a wide range of biological activities [1] such as antimalarials [1a], antifolates [1b-f] and antivirus [1g], as well as potential radiation protection agents. Several methodologies have been already developed to synthesize the furo[2,3-*d*]pyrimidine derivatives [2-13]. However, many of the synthetic protocols reported so far suffer from disadvantages, such as relying on multistep reactions [2], needing anhydrous conditions [3], prolonged reaction times [3-5], harsh reaction conditions [5], low yields [6-8], use of metal-containing reagents [9-10] and special instruments [11] or starting materials [12-13].

Propylphosphonic anhydride (T3P) has been identified as an efficient and reliable coupling agent and also a water scavenger [14] employed for the conversion of carboxylic acids, aldehydes, and amides to nitriles and formamides to isocyanides [15]. Recently, T3P/DMSO has received increased attention as oxidizing agent for *in situ* oxidation of alcohols [16]. This reagent offers several advantages such as high yields, purity, low toxicity, broad functional group tolerance, and easy work-up when compared to traditional reagents.

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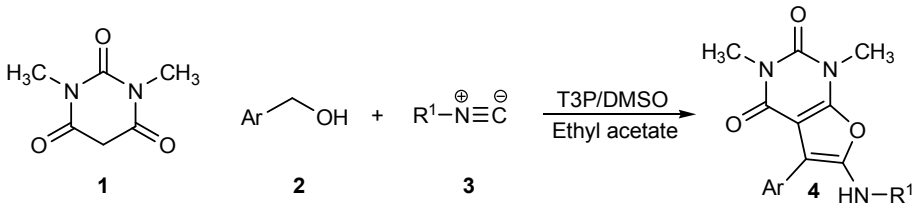
Recently, the isocyanide-based multi-component reactions (MCRs) have been reported for the synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones by the condensation of an aldehyde, an isocyanide and *N,N'*-dimethylbarbituric acid [17]. Though these protocols are quite useful, there is still a need to develop new methodologies which might work under milder reaction conditions. So far, there is no report on the one-pot synthesis of furo[2,3-*d*]pyrimidine directly from alcohols. Due to aforementioned reasons, and as a part of our ongoing research on isocyanide-based MCRs [18], here, we report an in situ tandem oxidation-cyclocondensation sequence reaction of, *N,N'*-dimethylbarbituric acid 1, alcohol 2 and various isocyanides for the preparation of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones 4 using T3P/DMSO as oxidant at 25 °C (Scheme 1). Thus, under oxidative conditions, alcohols converted into the corresponding aldehydes by T3P/DMSO. Subsequently, the in situ formed aldehyde is condensed with *N,N'*-dimethylbarbituric acid followed by treatment with isocyanide at 25 °C which resulted in the corresponding furo[2,3-*d*]pyrimidine 4.

EXPERIMENTAL PROCEDURES

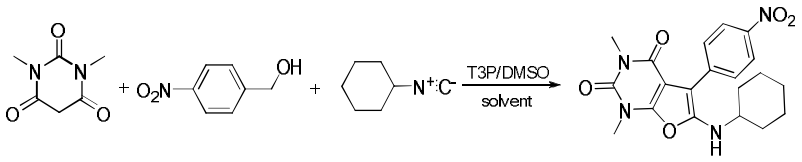
General Procedure for the Synthesis of Furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

To the solution of alcohol (1 mmol) in a mixture of



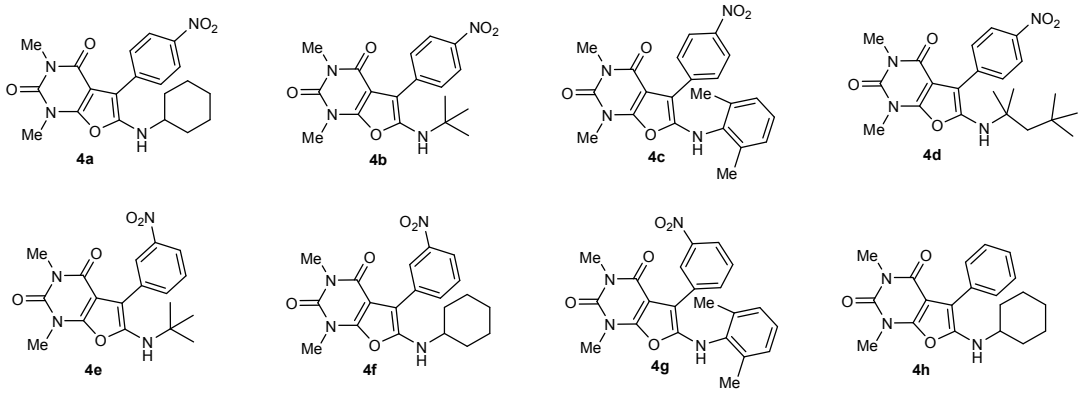
Scheme 1. Synthesis of furo[2,3-*d*]pyrimidine

Table 1. Optimization of the Reaction



Entry	Time (h)	T3P (equiv.)	EtOAc:DMSO	Temperature (°C)	Yield (%)
1	30	1	2:1	25	Trace
2	30	1.5	2:1	25	30
3	7	2	2:1	25	56
4	4	2.5	2:1	25	80
5	2.5	3	2:1	25	88
6	2.5	3.5	2:1	25	85
7	2.5	4	2:1	25	87
8	2.5	5	2:1	25	88
9	12	3	2:1	25	88
10	30	0	2:1	25	0
11	2.5	3	2:1	40	84
12	2.5	3	2:1	50	82
13	2.5	3	1:1	25	77
14	2.5	3	1:2	25	82
15	2.5	3	1:3	25	81
16	2.5	3	1:4	25	82

Table 2. Synthesis of 2-Aminofuran Derivatives[a]



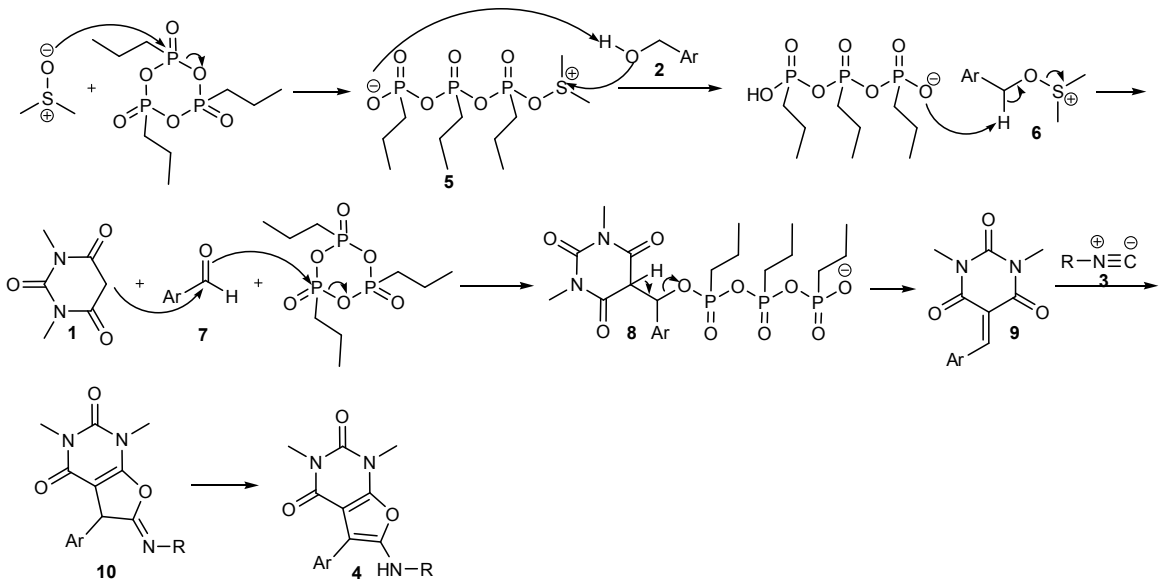
Entry	Alcohol	Isocyanide	Product	Yield (%)[b]	Ref.
1	4-Nitrobenzyl alcohol	Cyclohexylisocyanide	4a	88	[17]
2	4-Nitrobenzyl alcohol	tert-Butyl isocyanide	4b	82	[17]
3	4-Nitrobenzyl alcohol	2,6-Dimethylphenylisocyanide	4c	79	[17]
4	4-Nitrobenzyl alcohol	1,3,3-Tetramethylbutylisocyanide	4d	84	[17]
5	3-Nitrobenzyl alcohol	tert-Butyl isocyanide	4e	74	[17]
6	3-Nitrobenzyl alcohol	Cyclohexylisocyanide	4f	75	[17]
7	3-Nitrobenzyl alcohol	2,6-Dimethylphenylisocyanide	4g	71	[17]
8	Benzyl alcohol	Cyclohexylisocyanide	4h	74	[17]

[a]Reaction conditions: benzyl alcohol 2 (1 mmol), T3P (0.954 g, 3 mmol, 50% solution in ethyl acetate), EtAc (6 ml) and DMSO (3 ml) stirred at room temperature. After 2 h, *N,N'*-dimethylbarbituric acid 1 (1 mmol) and isocyanide 3 (1 mmol) were added and the mixture was stirred for 30 min at room temperature. [b]Isolated yield.

solvents ethyl acetate (6 ml) and DMSO (3 ml), was added T3P (0.954 g, 3 mmol, 50% solution in ethyl acetate) at 0 ^{o}C and the resulting reaction mixture was stirred at room temperature for 2 h. *N,N'*-dimethylbarbituric acid (1mmol) and isocyanide (1 mmol) were added and stirred for further 30 min. After completion of the reaction, the mixture was diluted with water (25 ml) and neutralized with 10% $NaHCO_3$ solution. The product was extracted with ethyl acetate (20 ml) and the combined organic phase was washed with water (10 ml). The organic phase was dried over anhydrous Mg_2SO_4. The solvent was dried under reduced pressure. The solid residue was recrystallized from CH_2Cl_2/ EtOH (1:2) to give the products.

RESULTS AND DISCUSSION

We chose the reaction of *N,N'*-dimethylbarbituric acid 1, 4-nitrobenzyl alcohol 2, cyclohexyl isocyanide as a model system for the optimization study. First, we studied the model reaction using T3P (3.0 equiv., 50% solution in EtOAc), without DMSO, at room temperature as well as 70 °C, however no reaction was observed; indicating that



Scheme 2. Proposed mechanism for the synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones

DMSO is an important component for the reaction. When the reaction was performed in T3P (3.0 equiv., 50% solution in EtOAc), and 2:1 volume of EtOAc:DMSO at room temperature, the corresponding product was obtained in good yield. Increasing the volume of DMSO in the ratios (EtOAc/DMSO) of 1:1, 1:2, 1:3, and 1:4 improved the yield of reaction, while increasing T3P to 3.5, 4 and 5 equiv. did not show a significant improvement. Next, we studied the model reaction in T3P (3.0 equiv., 50% solution in EtOAc), and 2:1 volume of EtOAc:DMSO at different temperatures. However, a further increase in the reaction temperature had an adverse effect. Further work indicated that the best results are obtained when the reaction is carried out at room temperature for 3 h using T3P (3.0 equiv., 50% solution in EtOAc), and 2:1 volume of EtOAc:DMSO.

Under the optimized conditions established above, we decided to probe the generality of this multicomponent reaction. A variety of isocyanides, such as cyclohexyl isocyanide, 1,3,3-tetramethylbutyl isocyanide, tert-butyl isocyanide, and 2,6-dimethylphenylisocyanide and various types of benzyl alcohols 2 such as 4-nitrobenzyl alcohol, 3-nitrobenzyl alcohol and benzyl alcohol were tested. Results in Table 2 clearly show that all reactions proceeded smoothly to afford the expected furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones in good yields [19].

A possible mechanism of the oxidative and dehydrative cyclization is suggested in Scheme 2 to get furo[2,3-*d*] pyrimidine-2,4(1*H*,3*H*)-diones. DMSO gets activated by T3P to give an electrophilic sulfur species 5, which then reacts with benzyl alcohol 2 to give an aryloxysulfonium salt 6. The hydrolyzed T3P acts as a base to pull out hydrogen of aryloxysulfonium salt 6 to form aldehyde 7. The second step in the probable mechanism is the T3P catalyzed condensation of *N,N′*-dimethylbarbituric acid with aldehyde to afford intermediate 8, which undergoes elimination to form the conjugated electron-deficient heterodiene 9, followed by a [1+4] cycloaddition reaction or a Michael-type addition reaction with isocyanide 3 to afford an iminolactone 10, which then isomerizes to yield the furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones 4.

CONCLUSIONS

We have developed an efficient and simple one-pot strategy for the synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-diones by in situ oxidation of alcohols to aldehydes followed by the three-component coupling of aldehyde, *N,N′*-dimethylbarbituric acid, and isocyanide. These high

yielding reactions display a good functional group tolerance, while the product isolation is very straightforward. We hope that this approach may be of value to others seeking for novel synthetic fragments with unique properties for medicinal chemistry programs.

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