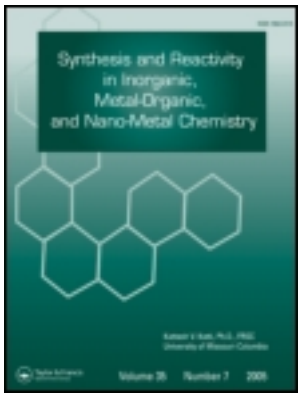

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An Efficient Solvent-Free Synthesis of Naphthopyranopyrimidines Using Heteropolyacid as an Ecofriendly Catalyst

Shivkumar S. Jalde [a], Hemant V. Chavan [b], Laxman K. Adsul [a], Valmik D. Dhakane [a] & Babasaheb P. Bandgar [a]

[a] Medicinal Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur, Maharashtra, India

[b] Department of Organic Chemistry, University of Mumbai, Ratnagiri sub-center, Ratnagiri, Maharashtra, India

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An Efficient Solvent-Free Synthesis of Naphthopyranopyrimidines Using Heteropolyacid as an Ecofriendly Catalyst

Shivkumar S. Jalde,[1] Hemant V. Chavan,[2] Laxman K. Adsul,[1] Valmik D. Dhakane,[1] and Babasaheb P. Bandgar[1]

[1]*Medicinal Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur, Maharashtra, India*
[2]*Department of Organic Chemistry, University of Mumbai, Ratnagiri sub-center, Ratnagiri, Maharashtra, India*

An efficient, one-pot, three-component synthesis of naphthopyranopyrimidines using β-naphthol, aldehydes, and 6-amino-1,3-dimethyl uracil catalyzed by heteropolyacid has been achieved within a short period of time. The present methodology offers several advantages such as ecofriendly catalyst, low catalyst loading, short reaction time, simple purification procedure, and excellent yields.

Keywords heteropolyacid, multicomponent reaction, naphthopyranopyrimidines

INTRODUCTION

Multicomponent reactions (MCRs) play an important role in modern synthetic organic chemistry because they generally occur in a single pot and exhibit a high atom-economy and selectivity. Multicomponent reaction reduces time and saves energy and raw material.[1] Over the past decade, various advanced sequential MCRs have been developed where 1,3-dicarbonyl derivatives are important synthetic intermediates due to its multiple functionalities that can be involved either as nucleophilic or electrophilic species in a large variety of synthetic transformation.[2] Their versatility and effectiveness as potential multicomponent substrates has been used in various MCRs such as Hantzsch 1,4-dihydropyridine synthesis,[3] Biginelli reaction,[4] and Michael addition reaction.[5]

Heteropolyacids (HPAs) have several advantages as a catalyst that make them economically and environmentally attractive. On one hand, HPAs have a very strong, approaching the super acid region, Brønsted acidity; on the other hand, they are efficient oxidants, exhibiting fast reversible multielectron redox transformations under mild conditions. HPAs have a very high solubility in polar solvents and fairly high thermal stability in the solid state. These properties render HPA as potentially promising acid, redox, and bifunctional catalyst in homogenous as well as in heterogenous systems.[6] They have been found to exhibit excellent catalytic properties in the isomerization of styrene oxide to phenylacetaldehyde,[7] synthesis of dihydroquinoline,[8] synthesis of arylbenzimidazoles,[9] Friedel-Craft alkylation,[10] tetrahydropyranylation of alcohols,[11] Prince reaction,[12] and Dakin-West reaction.[13]

Pyrimidine entity is one of the most prominent structures found in nucleic acid chemistry. Vitamin B_1 (thiamine) is well known example of naturally occurring pyrimidine that is encountered in our daily lives. There is continuous wide spread interest in pyranopyrimidines because of diverse biological activities such as antitumor,[14] antimicrobial,[15] and antihypertensive.[16] Pyranopyrimidines fused with coumarin ring are used as fungicides[17] and herbicides.[18] Naphthopyranopyrimidines are biologically important compounds with antimicrobial activity.[19] Neuropeptide S receptor, previously known as GPR-154, is highly expressed in brain areas that have been implicated in modulation of arousal, stress and anxiety. Therefore, Neuropeptide S receptor represents a novel drug target for the treatment of sleep and anxiety disorders.[20] Naphthopyranopyrimidines are selective antagonists of Neuropeptide S receptor (Figure 1). Though there is great importance of naphthopyranopyrimidines, only one report for the synthesis of naphthopyranopyrimidines by multicomponent condensation of β-napthol, aldehyde, and 6-amino-1,3-dimethyluracil using $InCl_3$ as an expensive catalyst is available in the literature.[21] More recently, Pravin Kumar et al. reported iodine catalyzed one-pot three-component synthesis of naphthopyranopyrimidines under solvent-free condition, long reaction time, and moderate yields are the notable drawbacks of this method.[22] Therefore, the development of

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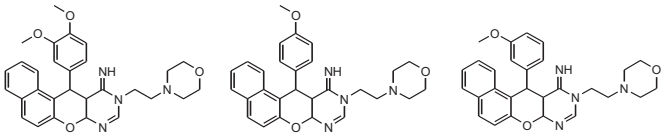
Address correspondence to Babasaheb P. Bandgar, Medicinal Chemistry Research Laboratory, School of Chemical Sciences, Solapur University, Solapur 413 255, Maharashtra, India. E-mail: bandgar_bp@yahoo.com

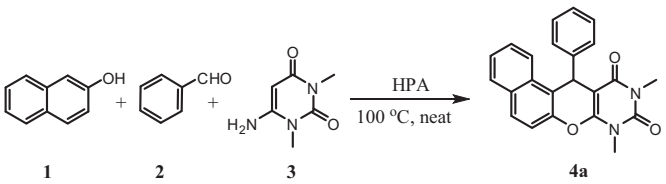


MLS000558527 NCGC00183145 NCGC00183146

FIG. 1. Selective antagonists of neuropeptide S receptor.

simple, efficient and high yielding protocol for the synthesis of naphthopyranopyrimidines is still desirable.

As a part of our research interest directed toward the development of highly expedient methods,[23] herein we report simple, efficient and environmentally benign synthesis of naphthopyranopyrimidines using silicotungstic acid ($H_4[SiW_{12}O_{40}]$) as an inexpensive catalyst under solvent-free condition (Scheme 1).



SCH. 1. Synthesis of naphthopyranopyrimidines.

EXPERIMENTAL

General Procedure for the Synthesis of Naphthopyranopyrimidines (4a–n)

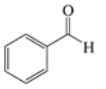
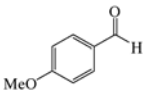
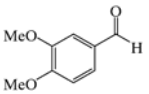
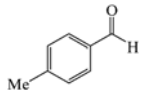
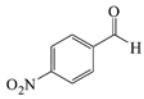
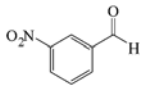
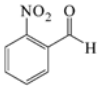
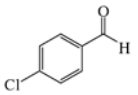
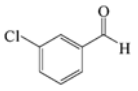
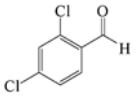
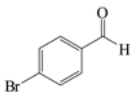
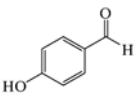
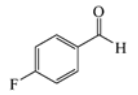
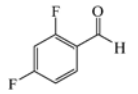
Silicotungstic acid (5 mol%) was added to a mixture of 2-naphthol (1.0 mmol), aldehyde (1.0 mmol), and 6-amino-1,3-dimethyl uracil (1.2 mmol) in a round-bottom flask, heated at 100°C under solvent-free condition. After completion of reaction (TLC), flask was cooled to room temperature, methanol (5 mL) was added and stirred for 10 min, poured over crushed ice, and the precipitated product was filtered, washed with water, dried, and recrystallized from methanol to obtain the desired product in pure form.

TABLE 1
The optimization of catalyst loading for the synthesis of naphthopyranopyrimidines

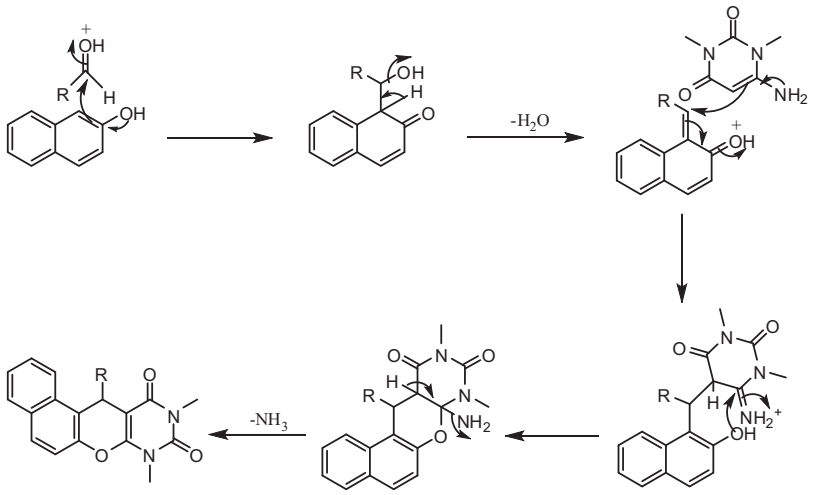
Entry	Catalyst	Catalyst (mol%)	Solvent	Temp (°C)	Time	Yield (%)[a]
1	—	—	—	100	12 h	NR[b]
2	$H_4[SiW_{12}O_{40}]$	5	Acetonitrile	Reflux	12 h	55
3	$H_4[SiW_{12}O_{40}]$	5	Methanol	Reflux	12 h	58
4	$H_4[SiW_{12}O_{40}]$	5	Toluene	Reflux	12 h	46
5	$H_4[SiW_{12}O_{40}]$	5	—	100	20 min	90
6	$H_4[SiW_{12}O_{40}]$	2	—	100	20 min	70
7	$H_4[SiW_{12}O_{40}]$	10	—	100	20 min	88
8	$H_4[SiW_{12}O_{40}]$	15	—	100	20 min	85

Reaction condition: β-naphthol (1.0 mmol), anisaldehyde (1.0 mmol), and 6-amino-1,3-dimethyluracil (1.2 mmol). [a]Isolated yield; [b]No reaction.

TABLE 2
Synthesis of naphthopyranopyrimidines

Entry	Aldehyde	Product	Time (min)	Yield (%)[a]
1		**4a**	20	90
2		**4b**	20	90
3		**4c**	29	88
4		**4d**	26	89
5		**4e**	24	90
6		**4f**	20	92
7		**4g**	27	88
8		**4h**	26	90
9		**4i**	23	91
10		**4j**	19	86
11		**4k**	27	89
12		**4l**	24	85
13		**4m**	23	90
14		**4n**	02	88

[a]Isolated yield.



SCH. 2. Proposed mechanism for the formation of naphthopyranopyrimidines.

12-(4-methoxyphenyl)-8,12-dihydro-8,10-dimethyl-9H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine-9,11-(10H)-dione (4b)

Solid; mp 257–259°C; IR (KBr, cm^{-1}): 3054, 2958, 1700, 1695, 1650, 1580, 1480; ^{1}H NMR (DMSO-d^6, 400 MHz): δ = 7.95 (d, 1H, J = 8.4 Hz), 7.84 (m, 2H), 7.50–7.31 (m, 3H), 7.28 (d, 2H, J = 8.0 Hz), 6.75 (d, 2H, J = 8.0 Hz), 5.76 (s, 1H), 3.85 (s, 3H), 3.62 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 161.4, 160.5, 158.5, 153.4, 153.1, 153.1, 135.2, 133.0, 129.4, 128.5, 128.0, 125.4, 122.8, 122.1, 118.2, 115.4, 114.6, 81.3, 56.0, 29.1, 28.9, 28.2; Mass: m/z = 401 [M+1].

12-(3-Nitrophenyl)-8,12-dihydro-8,10-dimethyl-9H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine-9,11-(10H)-dione (4f)

Solid; mp 310–312°C; IR (KBr, cm^{-1}): 3054, 2958, 1700, 1695, 1650, 1580, 1553, 1480,1340; ^{1}H NMR (DMSO-d^6, 400 MHz): δ = 8.12 (s, 1H), 8.05 (d, 1H, J = 8.2 Hz), 7.96–7.81 (m, 4H), 7.56–7.40 (m, 4H), 5.96 (s, 1H), 3.72 (s, 3H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 161.9, 159.8, 153.5, 152.8, 148.7, 143.6, 134.4, 133.4, 129.9, 128.7, 128.0, 125.9, 123.5, 122.8, 122.2, 121.1, 118.2, 115.4, 81.3, 29.1, 28.9, 27.5; Mass: m/z = 416 [M+1].

12-(4-Bromophenyl)-8,12-dihydro-8,10-dimethyl-9H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine-9,11-(10H)-dione (4k)

Solid; mp 250–252°C; IR (KBr, cm^{-1}): 3054, 2958, 1700, 1695, 1650, 1580, 1480; ^{1}H NMR (DMSO-d^6, 400 MHz): δ = 8.05 (m, 3H), 7.63 (d, 1H, J = 7.8 Hz), 7.52 (m, 2H), 7.38 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.2 Hz), 5.68 (s, 1H), 3.55 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 161.9, 159.8, 153.7, 153.2, 142.0, 133.4, 132.3, 130.6, 128.7, 128.0, 125.9, 122.8, 122.2, 120.6, 118.2, 115.4, 81.3, 29.1, 28.9, 27.7; Mass: m/z = 450 [M+2].

12-(3-Chlorophenyl)-8,12-dihydro-8,10-dimethyl-9H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidine-9,11-(10H)-dione (4i)

Solid; mp 250–252°C; IR (KBr, cm^{-1}): 3054, 2958, 1700, 1695, 1650, 1580, 1480; ^{1}H NMR (DMSO-d^6, 400 MHz): δ = 5.71 (s, 3H), 3.56 (s, 3H), 3.19 (s, 3H); 8.10 (m, 2H), 7.95 (d, 2H, J = 8.0 Hz), 7.69 (d, 1H, J = 8.0 Hz), 7.54 (m, 2H), 7.42 (s, 1H), 7.29 (m, 2H), 7.24 (d, 1H, J = 8.2 Hz), 5.71 (s, 1H), 3.56 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 161.4, 159.5, 153.7, 153.5, 144.4, 134.3, 133.4, 130.4, 128.8, 128.7, 128.0, 126.5, 126.4, 125.9, 122.8, 122.2, 118.2, 115.4, 81.3, 29.1, 28.7, 27.5; Mass: m/z = 404 [M+1].

RESULTS AND DISCUSSION

In order to evaluate the catalytic efficiency of $H_4[SiW_{12}O_{40}]$ and to determine the most appropriate reaction conditions; a model study was carried out using β-naphthol **1** (1 mmol), benzaldehyde **2** (1 mmol) and 6-amino-1,3-dimethyluracil **3** (1.2 mmol) to afford naphthopyranopyrimidine (**4a**) in different sets of reaction conditions. Initially, when the reaction was carried out in the absence of catalyst, no product formation was observed even after prolonged heating (Table 1, entry 1). Then the above model reaction was performed using catalytic amount of $H_4[SiW_{12}O_{40}]$ under solvent free condition, fortunately excellent yield (90%) of expected naphthopyranopyrimidine was observed in a very short reaction time (Table 1, entry 5).

Moreover, to evaluate the most appropriate catalyst loading, an identical reaction was performed using 2 mol%, 10 mol%, and 15 mol% of $H_4[SiW_{12}O_{40}]$ catalyst at 100°C under solvent-free condition, the yields were 70%, 88%, and 85% respectively (Table 1, entries 6–8). Therefore, 5 mol% of silicotungstic acid was sufficient to push the reaction forward, and, further, increasing the amount of silicotungstic acid did not increase the yields.

Then, we examined the effect of solvents such as acetonitrile, toluene, and methanol for the previous reaction, but poor yields were obtained after 12-h reflux (Table 1, entries 2–4). However, the best results were obtained under solvent free conditions (Table 1, entry 5).

In order to demonstrate the versatility of this protocol, we extended our study for the synthesis of wide variety of naphthopyranopyrimidines (**4a–n**) using a series of mono- and disubstituted aromatic aldehydes carrying either electron donating or electron withdrawing substitutions under the optimized reaction conditions (Table 2). All these reactions showed rapid formation of naphthopyranopyrimidine derivatives with high efficiency. Ortho substituted aldehydes furnished desired product with longer reaction time and low yields compared to their meta and para counterparts, this might be due to steric hindrance. We also studied the reactions of different aliphatic aldehydes such as propanal, hexanal, and cinnamaldehyde but unfortunately we failed to get the desired products.

Plausible mechanism for the formation of naphthopyranopyrimidines is outlined in Scheme 2, which proceeds *via* ortho quinine methide intermediate formation.

CONCLUSIONS

In conclusion, we have developed an efficient, solvent-free and environmentally benign process for the synthesis of naphthopyranopyrimidines by one-pot, three-component reaction of β-naphthol, aldehyde, and 6-amino-1,3-dimethyluracil catalyzed by silicotungstic acid as a readily available, economical, and environmentally safe catalyst. Mild reaction condition, low catalyst loading, excellent yields, simple purification, and ecofriendly catalyst are the major advantages of the present method.

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