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Microwave-assisted one-pot synthesis of octahydroquinazolinone derivatives using ammonium metavanadate under solvent-free condition

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Ammonium metavanadate (NH_4VO_3) has been shown to be an inexpensive, efficient, and mild catalyst for the one-pot synthesis of octahydroquinazolinone derivatives using dimedone, urea/thiourea, and appropriate aromatic aldehydes under microwave-irradiation.

In recent years, the Biginelli reaction has been employed for the synthesis of octahydroquinazolinones, which used cyclic β-diketones instead of open-chain dicarbonyl compounds. These octahydroquinazolinone derivatives have attracted considerable attention since they exhibit potent antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas* aeruginosa,[1] and calcium antagonist activity.[2,3]

Several methods have been developed for the preparation of quinazolinone derivatives. These routes usually involved reaction of aldehydes with $SOCl_2$ and pyridine, then with 2-aminobenzylamine in a refluxing solvent such as benzene or xylene with azeotropic water removal,[4] refluxing in ethanol/acetic acid mixture,[5]and by reaction in alkali media.

There are very few reports for the synthesis of octahydroquinazolinone derivatives using catalysts such as TMSCl,[6] Nafion-H,[7] concd H_2SO_4,[8] and ionic liquid[9] Octahydroquinazolinone derivatives are also synthesized in absolute ethanol but with low yields of products (19–69%).[2] However, many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged time period, poor yields, and use of hazardous and expensive catalysts. So the development of a clean, high-yielding, and environmentally friendly approach is still desirable. The use of ammonium metavanadate (NH_4VO_3) as an inorganic acid[10] meets the demand for an economic catalyst. It is employed similar to vanadium pentoxide[11] and as a catalyst in oxidation reactions with other cocatalysts.[12] It is a reagent used in analytical chemistry, photographic industry, and textile industry.[11] Gill and coworkers reported the synthesis of benzimidazole[13] and coumarin[14] in the presence of ammonium metavanadate. Very recently, we have reported the synthesis of α-hydroxyphosphonates[15] and α-aminophosphonates[16] using ammonium metavanadate as a catalyst in good yields.

During the last few years, 'non-classical' methods have been developed in organic synthesis in order to improve yields, selectivity, and experimental conditions.[17] Especially the use of microwave technology in conjunction with the use of solvent-free conditions allows expeditious and efficient procedures in organic synthesis.[18–21] However, great interest has been focused recently on 'dry media' synthesis using inorganic solid supports under microwave-irradiation. The coupling of a microwave heating mode with the use of solid acid has allowed the synthesis of several organic compounds, with higher purity of products and very simplified ease of manipulation and work-up. They clearly constitute an eco-friendly 'green' approach.[22]

The literature survey reveals that a number of octahydroquinazolinone derivatives have been synthesized by Biginelli reaction conditions using various aldehydes but not a single reference have been found where microwave-irradiation has been used.

In continuation of our research work of developing methods in various organic transformations,[23–25] we have developed a methodology for the synthesis of octahydroquinazolinone derivatives using ammonium metavanadate, which makes use of mild catalyst under microwave-irradiation and solvent-free conditions (Scheme 1).

The reaction of benzaldehyde (**1a**), dimedone (**2**), and urea (**3**) catalyzed by ammonium metavanadate under solvent-free conditions and microwave-irradiation has been considered as a standard model reaction.

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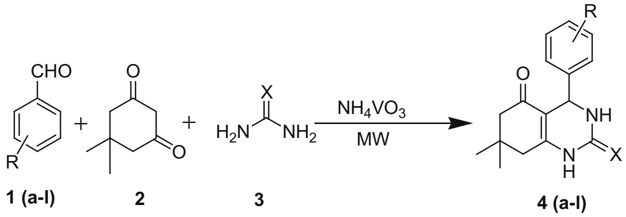

Scheme 1. Synthesis of octahydroquinazolinone derivaties

We also screened a number of different catalysts on the model reaction. When the reaction was carried out in the presence of KH_2PO_4, alum, acidic alumina, amberlite-IR 120, sulfamic acid, and cellulose sulfuric acid under microwave-irradiation it gave lower yield of product even after prolonged reaction time. However, when the same reaction was conducted under microwave-irradiation using ammonium metavanadate as a catalyst it gave excellent yields of product in short reaction time (Table 1, entry 6).

We have studied the catalyst concentration on model reaction. We have varied the concentration of catalyst to 5, 7, 10, and 12 mol %. The results revealed that when the reaction was carried out in the presence of 5 and 7 mol % of catalyst it gave lower yield of product even after prolonged reaction time. At the same time when the concentration of catalyst was 10 mol % we got excellent yields of product in a short span. Even after increasing the catalyst concentration at 12 mol %, the yields of the products were found to be constant. So, the use of 10 mol % of catalyst appears to be optimal. The results obtained are summarized in (Table 2).

Moreover, we investigated the effect of different microwave power settings such as 180, 360, 540, and 720 W. It was observed that the irradiation at low power required longer time and at high power suffered from lower yield. This indicates that the irradiation at 360 W gives better result (Table 3, entry 2).

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aldehydes, dimedone, and urea/thiourea using ammonium metavanadate as a catalyst under microwave-irradiation; the results are shown in Table 4. We have carried out similar reaction with various aromatic aldehydes containing electron-donating or electron-withdrawing functional groups at different positions but it did not show any remarkable differences in the yields of product and reaction time. It was observed that the reaction of aromatic aldehydes with urea is very fast as compared to thiourea. The results obtained in the current method are illustrated in Table 4.

Table 1
Screening of catalysts on the model reaction[a]

Entry	Catalysts	Time (min)	Yield[b] (%)
1	KH_2PO_4	15	20
1	Alum	15	65
2	Acidic alumina	15	52
3	Amberlite IR-120	15	68
4	Sulfamic acid	15	54
5	Cellulose sulfuric acid	15	63
6	Ammonium metavanadate	15	94

[a] Reaction of benzaldehyde, dimedone, and urea in the presence of ammonium metavanadate under microwave-irradiation and solvent-free condition.
[b] Isolated yield.

Table 2
Effect of catalyst concentration on model reaction[a]

Entry	Catalyst (mol %)	Yield[b] (%)
1	5	52
2	7	65
3	10	94
4	12	94

[a] Reaction of benzaldehyde, dimedone, and urea in the presence of ammonium metavanadate under microwave-irradiation and solvent-free condition.
[b] Isolated yield.

Table 3
Effect of microwave-irradiation powers for the synthesis of octahydroquinazolinone derivative **4a**[a]

Entry	Power (W)	Time (s)	Yield[b] (%)
1	180	70	87
2	360	50	94
3	540	40	86
4	720	30	82

[a] Compound **1a** (1 mmol) was treated with dimedone (1 mmol) and urea (1.5 mmol) in the presence of ammonium metavanadate (10 mol %) under microwave-irradiation.
[b] Isolated yield.

Table 4
Synthesis of octahydroquinazolinone derivatives catalyzed by ammonium metavanadate under microwave-irradiation[a]

Entry	RCHO	X	Time (min)	Yield[b] (%)	Mp (°C)
4a	H	O	6	94	290–293
4b	4-Cl	O	5	92	>300
4c	3-OMe, 4-OH	O	8	88	193–195
4d	3-NO_2	O	7	92	298–299
4e	3-OMe	O	8	86	248–249
4f	3-Cl	O	7	85	282–284
4g	4-NO_2	O	5	93	302–304
4h	4-F	O	7	90	134–136
4i	H	S	10	87	283–285
4j	4-OMe	S	12	83	275–276
4k	3-Cl	S	10	85	275–276
4l	4-Br	S	11	86	286–288

[a] Reaction condition: **1 (a–l)** (1 mmol), **2** (1 mmol), **3** (1.5 mmol) ammonium metavanadate (10 mol%), under microwave-irradiation.
[b] Isolated yield. All the products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR, and mass spectroscopy and also comprised the reference compounds.[6]

The role of NH_4VO_3 has been proposed to activate the aldehyde by binding the oxygen atom of aldehyde with vacant 'd' orbital of transition metal vanadium to achieve the stable oxidation state, Along with this we recovered the catalyst and reused for further reactions.[26]

In conclusion, ammonium metavanadate (NH_4VO_3) is a readily available, inexpensive, and efficient catalyst for the synthesis of octahydroquinazolinone derivatives. The advantages offered by this method are solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of octahydroquinazolinone derivatives.

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