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A novel multi-component synthesis of 4-arylaminoquinazolines

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ABSTRACT

A new multi-component synthesis of 4-arylaminoquinazolines from the reaction of 2-aminobenzamide, orthoesters, and substituted anilines in the presence of catalytic amounts of Keggin-type heteropolyacids is reported. The effects of reaction conditions and different heteropolyacids have been studied.

The development of methods using heteropolyacids (HPAs) as catalysts for the synthesis of fine chemicals, such as flavors, pharmaceuticals, and in food industries, has gained attention in the last decade.[1] Catalysts based on heteropolyacids have many advantages over liquid-acid catalysts. They are not corrosive and are environmentally benign and present fewer disposal problems. Solid heteropolyacids have attracted much attention in organic synthesis owing to easy work-up procedures, easy filtration, and reduction of cost and waste generation through reuse and recycling of the catalysts.[2]

Natural and synthetic compounds possessing the quinazoline structural motif display a wide range of biological activities. Recently, quinazolin-4(3*H*)-ones were prepared via cyclocondensation of 2-aminobenzamides with orthoesters catalyzed by SiO_2/H_2SO_4 under anhydrous and microwave conditions.[3] In other work, quinazolin-4(3*H*)-one and quinazolin-2,4-dione derivatives were obtained under microwave irradiation.[4]

There has been renewed interest in 4-arylaminoquinazolines connected with reports on the very high activity of 6,7-dimethoxy-4-(3-bromophenylamino)quinazoline (PD 153035) as a tyrosine kinase inhibitor.[5] Analogues of PD 153035 with more complex structures[6] as well as simple derivatives of 4-phenylaminoquinazoline without, for example, methoxy groups,[7] also show interesting biological activity. Despite their biological activities, no recent progress on their syntheses has been made.

4-Arylaminoquinazolines can be obtained via reactions of 4-halo- or 4-mercaptoquinazolines with aromatic amines;[8,9] however, the yields of these reactions do not usually[10] exceed 50%. 4-Arylaminoquinazolines have also been produced by reactions of 4(3*H*)-quinazolone with aromatic amine hydrochlorides in the presence of phosphorus pentoxide and dimethylcyclohexylamine.[11] 4-Phenylaminoquinazoline was obtained by desulfurization of 4-phenylaminoquinazol-2-thione using Raney nickel W7.[12]

In addition to the reactions mentioned above, 4-arylaminoquinazolines have been obtained by the reaction of 2-aminobenzonitrile and various anilines in the presence of $AlCl_3$, and by subsequent condensation of the products with formic acid.[13] The drawback of this method is that the synthesis of 2-amino-*N*-aryl-benzamidines is limited by the substituents on the anilines.

In connection with our research using heteropolyacids in organic reactions,[14–19] and expansion of our work on multi-component syntheses,[20] herein, we report a simple method for the preparation of 4-arylaminoquinazolines in high yields from the reaction of 2-aminobenzamide, orthoesters, and various substituted anilines in the presence of catalytic amounts of Keggin-type heteropolyacids: $H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, and $H_3[PMo_{12}O_{40}]$ (Scheme 1).

The reaction conditions (solvent, reaction time, and catalyst type) were studied to optimize this procedure. The results on the synthesis of 4-arylaminoquinazolines **1** from the reaction of 2-aminobenzamide, orthoesters, and various anilines, using $H_6[PMo_9V_3O_{40}]$, are summarized in Table 1. Anilines with electron-donating groups gave slightly better yields than anilines with electron-withdrawing groups.

In all the reactions, 3-quinazolin-4-one, 2, was obtained as a byproduct in low yield (Scheme 1). To optimize the yield of the de-

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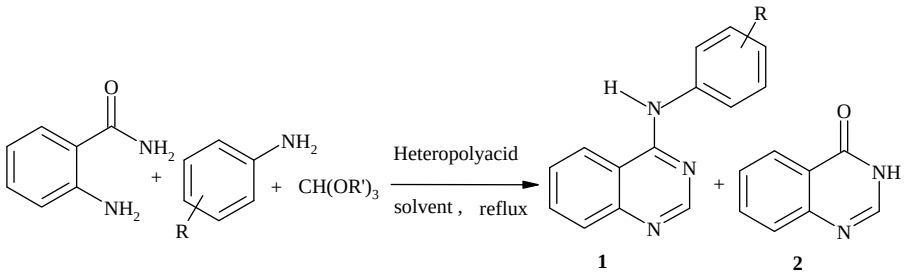

Scheme 1.

Table 1
Synthesis of various 4-arylaminoquinazolines

Entry	R	R′	Yield (%)[a]	Mp (°C)	Lit. mp (°C)[13]
1	H	C_2H_5	91	220	220–221
2	4-Me	C_2H_5	93	192	191–193
3	3,4-DiMe	C_2H_5	95	197	196.5–8
4	4-Cl	C_2H_5	89	194	194–195
5	4-Br	C_2H_5	88	190	189–190
6	2-Br	C_2H_5	85	131	131–132
7	H	CH_3	89	220	220–221
8	4-Me	CH_3	91	192	191–193
9	3,4-DiMe	CH_3	94	197	196.5–8
10	4-Cl	CH_3	87	194	194–195
11	4-Br	CH_3	85	190	189–190
12	2-Br	CH_3	82	131	131–132

[a] Yield refers to isolated products from the reaction of 2-aminobenzamide (10 mmol), substituted aniline (15 mmol), and $HC(OR')_3$ (10 mmol) in the presence of $H_6[PMo_9V_3O_{40}]$ (0.03 mmol) under reflux in CH_3CN.

sired product, the effects of reaction time, amount of aniline and solvent were investigated.

The effect of varying the reaction duration was studied for the synthesis of 4-arylaminoquinazolines by reaction of 2-aminobenzamide, $HC(OC_2H_5)_3$, and various anilines. The results are summarized in Table 2, and the optimum reaction time was found to be 2 h.

The amount of aniline required for reaction and to reduce the yield of **2** was investigated, and the results are summarized in Table 3. As shown, the optimum amount of aniline was 15 mmol in the presence of 10 mmol each of 2-aminobenzamide and orthoester.

Table 2
Synthesis of 4-arylaminoquinazolines by varying the reaction times

Entry	R	Time (h)	Yield (%) **1**[a]	Yield (%) **2**[a]
1	H	0.5	80	20
2	H	1	88	12
3	H	2	91	9
4	4-Me	0.5	80	20
5	4-Me	1	89	11
6	4-Me	2	93	7
7	3,4-DiMe	0.5	86	14
8	3,4-DiMe	1	91	9
9	3,4-DiMe	2	95	5
10	4-Cl	0.5	75	25
11	4-Cl	1	82	18
12	4-Cl	2	89	11
13	4-Br	0.5	75	25
14	4-Br	1	80	20
15	4-Br	2	88	12
16	2-Br	0.5	73	27
17	2-Br	1	80	20
18	2-Br	2	85	15

[a] Yield refers to isolated products from the reaction of 2-aminobenzamide (10 mmol), substituted aniline (15 mmol), and $HC(OC_2H_5)_3$ (10 mmol) in the presence of $H_6[PMo_9V_3O_{40}]$ (0.03 mmol) under refluxing conditions in CH_3CN.

Table 3
Effect of varying the amounts of aniline on the yields of 4-phenylaminoquinazolines

Entry	Time (h)	(mmol)	Yield[a] (%)
Aniline			
1	2.5	10	83
2	2.5	12	87
3	2	15	91
4	2	20	91

[a] Yield refers to isolated products from the reaction of 2-aminobenzamide (10 mmol), various amounts of aniline and $HC(OC_2H_5)_3$ (10 mmol) in the presence of $H_6[PMo_9V_3O_{40}]$ (0.03 mmol) under refluxing conditions in CH_3CN.

The effect of solvent on the synthesis of different 4-arylaminoquinazolines was also studied. Of solvents including CH_3CN, H_2O, CH_2Cl_2, $CHCl_3$, and EtOH, CH_3CN proved to be the best in terms of yield, Table 4.

To study the effect of catalyst type, the synthesis of 4-benzylaminoquinazoline was selected as a model reaction and the efficiency using four Keggin-type heteropolyacids ($H_6[PMo_9V_3O_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_4[PMo_{11}VO_{40}]$, and $H_3[PMo_{12}O_{40}]$) was studied. The results are reported in Table 5 with the order of efficiency as follows: $H_6[PMo_9V_3O_{40}] > H_5[PMo_{10}V_2O_{40}] > H_4[PMo_{11}VO_{40}] > H_3[PMo_{12}O_{40}]$.

In conclusion, we have reported a new catalytic method for the synthesis of 4-arylaminoquinazolines from reactions of 2-aminobenzamide, orthoesters, and substituted anilines in the presence

Table 4
Effect of varying the solvent on the yield of 4-arylaminoquinazolines

Entry	R	Solvent	Time (h)	Yield (%)[a]
1	H	CH_3CN	2	91
2	H	CH_2Cl_2	2.5	87
3	H	$CHCl_3$	2.5	85
4	H	H_2O	2.5	83
5	H	EtOH	2.5	82
6	4-Me	CH_3CN	2	93
7	4-Me	CH_2Cl_2	2.5	90
8	4-Me	$CHCl_3$	2.5	88
9	4-Me	H_2O	2.5	87
10	4-Me	EtOH	2.5	85

[a] Yield refers to isolated products from the reaction of 2-aminobenzamide (10 mmol), substituted aniline (15 mmol), and $HC(OC_2H_5)_3$ (10 mmol) in the presence of $H_6[PMo_9V_3O_{40}]$ (0.03 mmol) under refluxing conditions.

Table 5
Effect of various Keggin-type heteropolyacids on the yields of 4-phenylaminoquinazolines

Entry	Catalyst	Time (h)	Yield (%)[a]
1	$H_6[PMo_9V_3O_{40}]$	2	91
2	$H_5[PMo_{10}V_2O_{40}]$	2.5	88
3	$H_4[PMo_{11}VO_{40}]$	2.5	85
4	$H_3[PMo_{12}O_{40}]$	3	81

[a] Yield refers to isolated products from the reaction of 2-aminobenzamide (10 mmol), substituted aniline (15 mmol), and $HC(OC_2H_5)_3$ (10 mmol) in the presence of $H_6[PMo_9V_3O_{40}]$ (0.03 mmol) under refluxing conditions in CH_3CN.

Table 6
A comparison of the efficiency of $H_6[PMo_9V_3O_{40}]$ on the synthesis of 4-arylaminoquinazolines over three runs

Entry	R	Time (min)/run			Yield (%)[a]/run		
		First	Second	Third	First	Second	Third
1	H	160	165	165	91	89	87
2	4-Me	160	165	165	93	93	91
3	3,4-DiMe	160	165	170	95	93	92
4	4-Cl	160	165	165	89	88	87
5	4-Br	160	165	170	88	87	86
6	2-Br	160	165	170	85	84	83

[a] Yield refers to isolated products from the reaction of 2-aminobenzamide (10 mmol), substituted aniline (15 mmol), and $HC(OC_2H_5)_3$ (10 mmol) in the presence of $H_6[PMo_9V_3O_{40}]$ (0.03 mmol) under refluxing conditions in CH_3CN.

of catalytic amounts of Keggin-type heteropolyacids as efficient, reusable, and eco-friendly heterogeneous inorganic catalysts. The advantages of this method are the easy work-up procedure and high yields of products.

General procedure for the synthesis of 4-arylaminoquinazolines: To a mixture of 2-aminobenzamide (10 mmol), orthoester (10 mmol), and substituted aniline (15 mmol), a catalytic amount of heteropolyacid (0.03 mmol) was added and the resulting mixture was heated at reflux in CH_3CN (10 mL). The progress of the reaction was monitored by TLC. On completion, the catalyst was filtered off, the solvent was evaporated and the pure product was obtained by column chromatography. All the products were identified by comparison of their physical and spectroscopic data with those reported for authentic samples.[13,21]

Recyclability of the catalyst: At the end of the reaction, the catalyst could be recovered by filtration. The recycled catalyst was washed with dichloromethane and used in a second run. To confirm that the catalyst was not soluble in the reaction solvent, the filtered catalyst was weighed before reuse. The results indicated that the catalysts were not soluble in the solvent, and the yields of reactions using these catalysts over three runs indicated only a slight loss of activity (Table 6).

Physical and spectral data for selected compounds: Phenyl-quinazolin-4-yl-amine ($C_{14}H_{11}N_3$): mp: 220 °C, ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 9.10 (s, 1H, NH) 8.68 (s, 1H, CH=N), 7–7.5 (m, 5H), 7.6–7.9 (m, 4H); FT-IR: 3329 (NH), 1604 (C=N); MS: *m/z* 221 [M^+].

Quinazolin-4-yl-p-tolyl-amine($C_{15}H_{13}N_3$): Mp: 192 °C, ^{1}H NMR (300 MHz, DMSO-*d*, δ ppm): 9.10 (s, 1H, NH), 2.33 (s, 3H, CH_3) 8.68 (s, lH, CH=N), 7–7.32 (m, 4H), 7.59–7.9 (m, 4H); FT-IR: 3329 (NH), 1604 (C=N); MS: *m/z* 235 [M^+].

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