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One-Pot Multi Component Synthesis of 4-Arylaminoquinazolines in the Presence of Sodium 30-Tungstopentaphosphate

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A new multi-component synthesis of 4-arylaminoquinazolines from the reaction of 2-aminobenzamide, orthoesters and substituted anilines in presence of catalytic amounts of sodium 30-tungstopentaphosphate, so-called Preyssler heteropolyacid, is reported. The effects of solvent, amount of catalyst and aniline and reaction time were studied. Optimum conditions for synthesis of 4-arylaminoquinazolines have been obtained.

Key Words: 4-Arylaminoquinazolines, Recyclable catalyst, Heteropolyacid, Preyssler.

INTRODUCTION

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[1]. In other work, quinazolin-4(3*H*)-one and quinazolin-2,4-dione derivatives were obtained under microwave irradiation[2].

Among the quinazolines, 4-arylaminoquinazolines are very important and can be obtained *via* reactions of 4-halo or 4-mercapto quinazolines with aromatic amines[3,4], 4(3*H*)-quinazolone with aromatic amine hydrochlorides in the presence of phosphorus pentoxide and dimethyl cyclohexylamine[5], desulfurization of 4-phenylaminoquinazol-2-thione using Raney nickel W7[6], the reaction of 2-aminobenzonitrile and various anilines in the presence of $AlCl_3$ and subsequent condensation of products with formic acid[7]. Despite of their interesting biological activities, no recent progress on their syntheses has been published.

In addition, the drawback of these methods is low yields and limitation for the substituents.

For this reason, there is still a good scope for research towards finding new methods with green and eco-friendly catalysts. It was shown that some heteropolyanions exhibited interesting catalytic properties as green and eco-friendly catalysts for both redox and/or acid-base type reactions in industrial applications[8,9]. Thus the development of methods using heteropolyacids (HPAs) as catalysts for the synthesis of fine chemicals, have gained attention in the last decade[10]. Catalysts based on heteropolyacids have many advantages over liquid acid catalysts. They are not corrosive and are environmentally benign and present fewer disposal problems.

Until now, most of fundamental investigations and all practical applications used, Keggin heteropolyacids, with the general formula[11-13] of $[XM_{12}O_{40}]^{p-}$. In recent years, interest in other heteropolyacids has been grown. One of the most important kinds of heteropoly acids is $[NaP_5W_{30}O_{110}]^{14-}$, so-called Preyssler's anion, which has formed by five PW_6O_{22} units arranged in a crown (Fig. 1). Recently, we have developed a series of Preyssler catalyzed reactions in organic chemistry[14-22]. We are interested on developing of applications of Preyssler in other areas because of its exclusive structure and properties.

Therefore, it is interest to know, what occurs if the Preyssler's anion has been used in the synthesis of 4- arylaminoquinazolines. In connection with our research using heteropolyacids in organic reactions[23-27] and expansion of our work on multicomponent syntheses[28], 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 Preyssler heteropolyacid.

EXPERIMENTAL

All of the chemicals were obtained from commercial sources. Preyssler heteropolyacid was prepared by passage of a solution of the potassium salt in water through a column

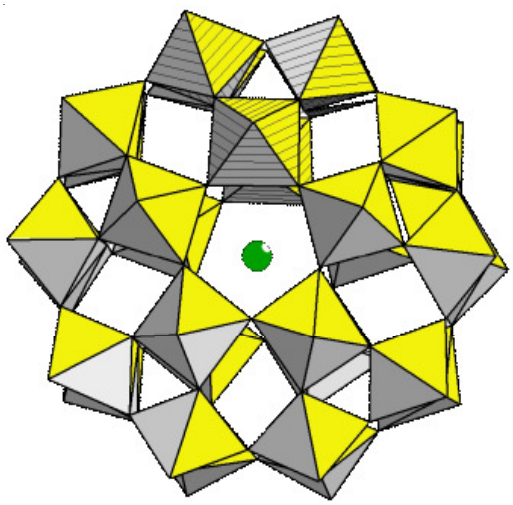
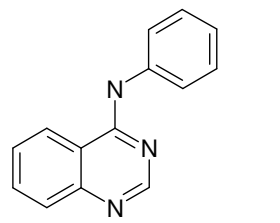
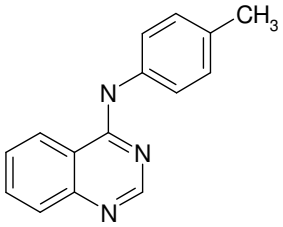


Fig. 1. Structure of Preyssler's anion

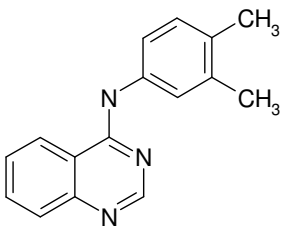
(50 cm × 1 cm) of Dowex 50W × 8 in the H^+ form and evaporation of the elute to dryness under vacuum. All yields were calculated from purified products. IR spectra were obtained with a Bruker 500 scientific spectrometer. ^{1}H NMR spectra were recorded on a FT NMR 300 Hz spectrometer. Melting points were obtained on a Electro thermal type 9100 apparatus. The structure of obtained products are shown in **Scheme-I**.



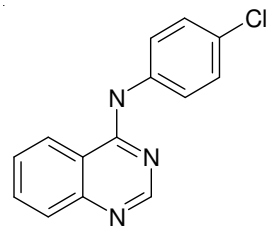
(a) phenyl-quinazolin-4-yl-amine



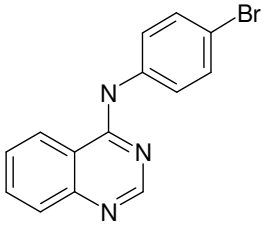
(b) quinazolin-4-*p*-tolyl-amine



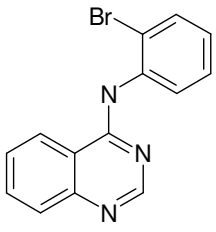
(c) Quinazolin-4-(3,4-dimethyl-phenyl)-amine



(d) Quinazolin-4-(4-chlorophenyl) -amine



(e) Quinazolin-4-(4-bromophenyl)-amine



(f) Quinazolin-4-(2-bromophenyl)-amine

Scheme-I

Physical and spectral data for selected compounds: Phenyl-quinazolin-4-yl-amine ($C_{14}H_{11}N_3$), m.p. 220 °C, ^{1}H NMR (500 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 ν(NH), 1604 ν(C=N).

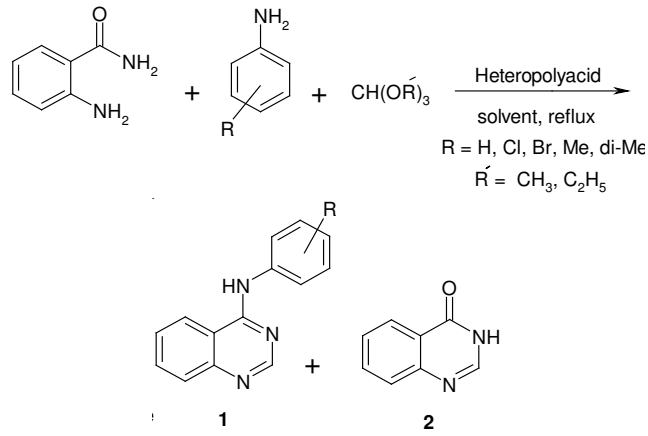
Quinazolin-4-yi-*p*-tolyl-amine ($C_{15}H_{13}N_3$), m.p. 192 °C, ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 9.10 (s, 1H, NH), 2.33 (s, 3H, CH_3), 8.68 (s, 1H, CH=N), 7-7.32 (m, 4H), 7.59-7.9 (m, 4H); FT-IR: 3329 ν(NH), 1604 ν(C=N).

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 refluxed 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.

Recycability of the catalyst: At the end of the reaction, the catalyst could be recovered by filtration. The recycled catalyst was used in a second run. The catalyst over five runs showed only a slight loss of activity (3-5 %).

RESULTS AND DISCUSSION

4-Arylaminoquinazolines (**1**) were synthesized *via* the reaction of 2-aminobenzamide, orthoesters and various anilines, using Preyssler with formula of $[NaP_5W_{30}O_{110}]^{14-}$. The Preyssler catalyst structure is shown in Fig. 1. The reaction is shown in **Scheme-II**. In all the reactions, 3-quinazolin-4-one (**2**) was obtained as a by product in low yield.



Sscheme-II

2-Aminobenzamide, $HC(OC_2H_5)_3$ and aniline were selected as optimized and model reactants for synthesis of 4- arylaminoquinazolines in acetonitrile as solvent. The amount of required aniline for reaction was investigated and the results are summarized in Fig. 2. As we can see, the optimum amount of aniline is 15 mmol.

After then, the effect of solvent on the synthesis of different 4-arylaminoquinazolines was studied. Acetonitrile, water, dichloromethane and ethanol were selected as solvents. Among

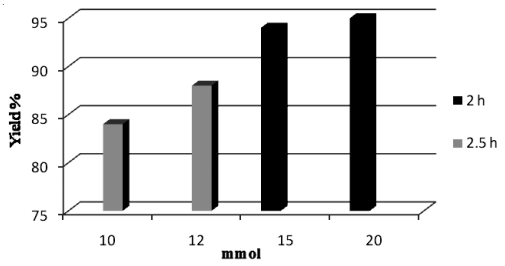


Fig. 2. Effect of varying the amount of anilines on the yields of 4-phenylaminoquinazolines.

these solvents acetonitrile proved to be the best in terms of yield (Table-1). For further study we selected two other reactants and found this result for two other selected reactants (Table-2, entries 5-12). The results in Table-1 show that in every case, the optimum reaction time is 2 h. A systematic study was performed for studying of reaction time. Data are shown in Table-2. In all of the experiments, the optimum reaction time was found to be 2 h.

TABLE-1
EFFECT OF VARYING THE SOLVENT ON THE YIELDS OF 4-ARYLAMINOQUINAZOLINES

Entry	R	Solvent	Time (h)	Yield (%)*
1	H	CH_3CN	2.0	91
2	H	CH_2Cl_2	2.5	86
3	H	H_2O	2.5	85
4	H	EtOH	2.5	80
5	4-Me	CH_3CN	2.0	94
6	4-Me	CH_2Cl_2	2.5	90
7	4-Me	H_2O	2.5	87
8	4-Me	EtOH	2.5	86
9	4-Cl	CH_3CN	2.0	90
10	4-Cl	CH_2Cl_2	2.5	85
11	4-Cl	H_2O	2.5	84
12	4-Cl	EtOH	2.5	79

*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)

TABLE-2
SYNTHESIS OF 4-ARYLAMINOQUINAZOLINES BY VARYING THE REACTION TIMES UNDER REFLUXING CONDITIONS

Entry	R	Time (h)	Yield (%)*
1	H	0.5	79
2	H	1.0	87
3	H	2.0	91
4	4-Me	0.5	82
5	4-Me	1.0	89
6	4-Me	2.0	94
7	3,4-diMe	0.5	77
8	3,4-diMe	1.0	90
9	3,4-diMe	2.0	96
10	4-Cl	0.5	74
11	4-Cl	1.0	82
12	4-Cl	2.0	90
13	4-Br	0.5	73
14	4-Br	1.0	80
15	4-Br	2.0	89
16	2-Br	0.5	70
17	2-Br	1.0	79
18	2-Br	2.0	83

*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 CH_3CN.

One of the important factors effecting the behaviour of HPAs, is the energy gap between the highest accupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The HPAs are easily reducible chemical species and thus the energy of the LUMO must be sufficiently low to accept the incoming electron in electron transfer reactions. The solvent molecules stabilize HPAs and place these molecular orbitals at the appropriate level. We believe that, the energy and composition of the LUMOs have significant effects on the activity of the studied HPAs.

To determine the optimum amount of catalyst, different amounts including, 0.01, 0.02, 0.03 and 0.04 mmol were investigated. The results are shown in Table-3. It is clear that the yields depend on the amount of catalyst, the optimum amount of which was 0.03 mmol for all derivatives. Increase in this amount has not any effect on the obtained yields. Under optimum conditions, synthesis of various 4-arylaminoquinazolines has been studied in the presence of Preyssler catalyst. The results are shown in Table-4. The data in this table show that Preyssler can catalyze the synthesis of 4-arylaminoquina-zolines in excellent yields.

TABLE-3
EFFECT OF VARYING THE AMOUNT OF CATALYST ON THE YIELDS OF 4-ARYLAMINOQUINAZOLINES

Entry	Catalyst	(mmol)	Time (h)	Yield (%)*
1	$H_{14}[NaP_5W_{30}O_{110}]$	0.01	2	82
2	$H_{14}[NaP_5W_{30}O_{110}]$	0.02	2	85
3	$H_{14}[NaP_5W_{30}O_{110}]$	0.03	2	91
4	$H_{14}[NaP_5W_{30}O_{110}]$	0.04	2	91

*Yield refers to isolate 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 varying the amount of Preyssler heteropolyacid under refluxing conditions in CH_3CN.

TABLE-4
SYNTHESIS OF VARIOUS 4-ARYLAMINOQUINAZOLINES AT REFLUX

Entry	R	R'	Yield (%)	m.p. (ºC)	Lit.[7] m.p. (ºC)
1(a)	H	C_2H_5	91	221	220-221
2(b)	4-Me	C_2H_5	94	191	191-193
3(c)	3,4-diMe	C_2H_5	96	197	196-198
4(d)	4-Cl	C_2H_5	90	195	194-195
5(e)	4-Br	C_2H_5	89	190	189-190
6(f)	2-Br	C_2H_5	85	131	131-132
7(a)	H	CH_3	90	221	220-221
8(b)	4-Me	CH_3	93	191	191-193
9(c)	3,4-diMe	CH_3	96	197	196-198
10(d)	4-Cl	CH_3	89	195	194-195
11(e)	4-Br	CH_3	87	190	189-190
12(f)	2-Br	CH_3	83	131	131-132

Yield refers to isolate products from the reaction of 2-aminobenzamide (10 mmol), substituted anilines (15 mmol) and $HC(OR')_3$ (10 mmol) in the presence of Preyssler (0.03 mmol) under reflux in CH_3CN.

Reusability of the catalyst: In present studies it has been found that Preyssler's anion catalyzes organic reactions without any degradation of structure. This leads to the recovery and recyclibility of catalyst, which is very important in catalytic processes, especially, in industry. Fig. 3 shows the IR spectrum of Preyssler's anion before (a) and after (b) catalytic reaction.

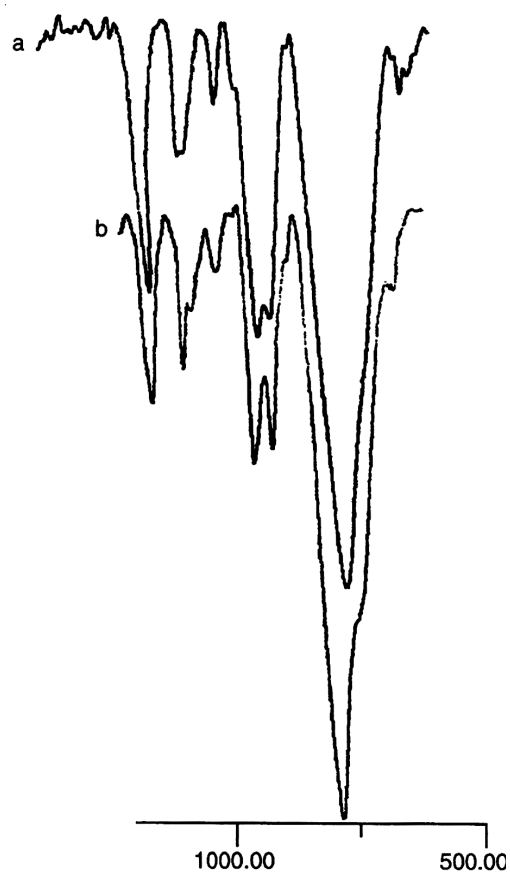


Fig. 3. IR spectrum of Preyssler's anion before (a) and after (b) catalytic reaction

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 of catalytic amounts of Preyssler-type heteropolyacid as efficient, reusable and eco-friendly heterogeneous inorganic catalyst. The advantages of this method are the easy work-up procedure and high yields of products. We are continuing to study for synthesis of other heterocycles using Preyssler catalyst with the aim of developing environmentally benign chemical processes and extending Preyssler application.

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