



Pentafluorophenylammonium Triflate: An Efficient, Practical and Environmental Friendly Catalyst for Synthesis of Quinazolin-4(3H)-ones

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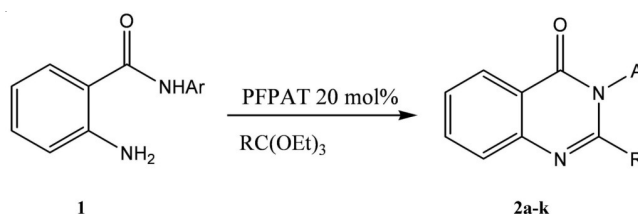
An efficient, solvent-free, clean and facile synthesis of 2,3-disubstituted quinazolin-4(3H)-ones from cyclocondensation of 2-aminobenzamides with orthoesters catalyzed by pentafluorophenylammonium triflate under microwave irradiation conditions is described.

Key Words: Quinazolin-4(3H)-ones, Pentafluorophenylammonium triflate, Solvent-free.

INTRODUCTION

Quinazolines and especially quinazolinones have long been the subject of numerous studies on account of their pharmaceutical and biological properties¹⁻⁸. Over the years despite the extensive efforts that have been paid to the synthesis of quinazolin-4(3H)-ones various methods have already been proposed for the synthesis of these compounds⁹. The most general method for synthesis of these compounds involves cyclocondensation of anthranilamides with aldehydes in presence of various promoting agents, such as Sc(OTf)₃¹⁰, *p*-toluenesulfonic acid/DDQ¹¹, I₂/KI in water¹², CuCl₂ in ethanol¹³ and KMnO₄ under microwave irradiation¹⁴. Other methods such as cyclocondensation of 2-aminobenzamides with substituted benzoyl chlorides¹⁵, one pot reaction of isatoic anhydride, ammonium acetate and aldehydes using Ga(OTf)₃¹⁶ or I₂ under solvent-free conditions¹⁷, three-component coupling of anthranilic acid, amines and orthoesters¹⁸ and reaction of benzoxazine-4-ones with primary amines under microwave irradiation¹⁹ are also reported for the synthesis of these compounds. However, some of these procedures have disadvantages, for example use of expensive acid catalysts in organic solvents, long reaction times and tedious work up. Hence, the development of efficient high-yielding and environmentally friendly protocols using a new catalyst for the synthesis of these compounds is still desirable and is important. Although these methods are effective, but some of them suffer from either a tedious synthetic methodology, or requirement of a large amount of catalyst to complete the reaction. Funatomi *et al.*²⁰ reported the application of pentafluorophenylammonium triflate (C₆F₅NH₃⁺.OTf, PFPAT) as a novel organocatalyst in organic transformation

such as estrification of carboxylic acids with alcohols, C-acylations of enolsilyl ethers or ketensilyl(thio)acetals with acid chlorides²¹ and Mukaiyamaaldol and Mannich reactions using ketensilylacetals with ketenes and oxime ethers²². Recently we reported our research finding on the application of pentafluorophenylammonium triflate as catalyst in the synthesis of coummarines *via* Von Pechman condensation²³. As a part of our ongoing research to develop efficient and environmentally benign synthetic methods in organic chemistry²⁴⁻²⁶, herein, we report the first example of the pentafluorophenylammonium triflate-catalyzed one-pot synthesis of quinazolin-4(3H)-ones. Therefore under microwave irradiation and solvent-free conditions 2-aminobenzamides **1** reacted with triethylorthoesters in the presence of 20 mol % pentafluorophenylammonium triflate. After 6 min the reactions are completed and quinazolin-4(3H)-ones **2** derivatives prepared in high yields (**Scheme-I**).



Scheme-I: Synthesis of 2,3-disubstituted quinazolin-4(3H)-ones

EXPERIMENTAL

All products were known compounds and identified by comparison with authentic samples. The catalyst is prepared according to the literature²⁰. 2-Aminobenzamides **1** were

prepared according to a reported procedure from the readily available isatoic anhydride and the proper primary amines²⁷. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Infrared spectra (ν cm^{-1}) were recorded on Shimadzu IR-470, using KBr disks. ¹H NMR spectra were recorded on DRX-500 MHz NMR Spectrometer at 293 K in CDCl_3 . Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. The NMR and IR spectra of the products were in agreement with earlier data. Microwave synthesizer; (Questron Technologies Corp., Canada; model- ProM) having monomode open-vessel was used for the synthesis.

General procedure for the synthesis of 2,3-disubstituted quinazolin-4(3H)-ones (2a-2k): A mixture of **1** (2 mmol), orthoester **2** (2 mL in each case) and 20 mol % of finely ground pentafluorophenylammonium triflate was subjected to microwave irradiation at 210 and 385W for 2 and 4 min respectively. The progress of reaction was monitored by TLC. Upon completion, the hot residue was dissolved in 10 mL of 95 % ethanol. The solid catalyst was filtered off and the fairly pure crystals of products that separated on cooling from the filtrate solution were further recrystallized in ethanol 95 %. The selected spectral data of five synthesized compounds are given below:

2-Methyl-3-phenyl-4(3H)quinazoline (2b): m.p.: 145-146 °C; IR (KBr, ν_{max} , cm^{-1}) 3040 (CH, arom), 1668 (C=O), 1595 (C=N); ¹H NMR (400 MHz, CDCl_3); 2.26 (s, 3H, CH_3), 7.25-8.30 (m, 9H, Arom) ppm.

2-Methyl-3(4-ethyl phenyl)-4(3H)quinazoline (2g): m.p.: 150-151 °C; IR (KBr, ν_{max} , cm^{-1}) 3045 (CH, arom), 2960 (CH, aliph), 1681 (C=O), 1588 (C=N); ¹H NMR (400 MHz, CDCl_3); 1.32 (t, 3H, $J = 7.14$, CH_3), 2.28 (s, 3H, CH_3), 2.75 (q, 2H, $J = 7.14$, CH_2), 7.16-8.30 (m, 8H, arom) ppm.

2-Methyl-3(4-methyl phenyl)-4(3H)quinazoline (2h): m.p.: 150-152 °C; IR (KBr, ν_{max} , cm^{-1}) 3025 (CH, arom), 2986 (CH, aliph), 1684 (C=O), 1580 (C=N); ¹H NMR (400 MHz, CDCl_3); 2.32 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.18-8.38 (m, 8H, arom) ppm.

2-Ethyl-3(4-methyl phenyl)-4(3H)quinazoline (2i): m.p.: 159-161 °C; IR (KBr, ν_{max} , cm^{-1}) 3095 (CH, arom), 2992 (CH, aliph), 1688 (C=O), 1590 (C=N); ¹H NMR (400 MHz, CDCl_3); 1.26 (t, 3H, $J = 7.12$, CH_3), 2.51 (s, 3H, CH_3), 2.78 (q, 2H, $J = 7.12$, CH_2), 7.16-8.30 (m, 8H, arom) ppm.

3-benzyl-4(3H)quinazoline (2k): m.p.: 116-118 °C; IR (KBr, ν_{max} , cm^{-1}) 3045 (CH, arom), 2940 (CH, aliph), 1673 (C=O), 1578 (C=N); ¹H NMR (400 MHz, CDCl_3); 2.88 (s, 2H, CH_2), 6.88 (s, 1H), 7.22-8.38 (m, 8H, arom) ppm.

RESULTS AND DISCUSSION

To develop the methodology utilizing ammonium triflate catalysts, we focused our attention on some practical issues from the recent green chemical standpoint; (i) high reactivity, (ii) total cost effectiveness, (iii) easy preparation, handling, stability and moisture insensitivity of the catalyst and (iv) convenient removal of the catalyst from the reaction mixture, we chose a novel pentafluorophenylammonium triflate catalyst. Prompted by these findings and in continuation of our previous works to synthesis of heterocyclic compounds²⁸⁻³⁰, in this paper we wish to report a new green approach for the synthesis of 2,3-disubstituted quinazolin-4(3H)-ones **2a** (Table-1), through

cyclocondensation of 2-aminobenzamides derivatives **1** with orthoesters using pentafluorophenylammonium triflate as catalyst under microwave irradiation and solvent-free conditions (**Scheme-I**). Bronsted-acid, pentafluorophenylammonium triflate ($\text{C}_6\text{F}_5\text{NH}_3^+\text{OTf}^-$) was prepared according to the literature procedure²⁰, the pentafluorophenylammonium triflate prepared with this method have enough purity to applied as catalyst in organic reactions²⁰⁻²³. Initially, the reaction of 2-aminobenzamide 1 (Ar=Ph) with triethylorthoformate was selected as a model reaction to optimize the reaction conditions. The efficiency of the reaction is affected mainly by the amount of pentafluorophenylammonium triflate (Table-1). A trace amount of product was obtained in the absence of the catalyst even after 50 min, (Entry 1) indicating that the catalyst is necessary for the reaction. Increasing the amount of the catalyst increased the yield of the product **2a**. The optimal amount of the catalyst was 20 mol % (Entry 4); increasing the amount of the catalyst beyond this value did not increase the yield noticeably (Entries 5 and 6).

TABLE-1
EFFECT OF THE AMOUNT OF PFPAT ON THE MODEL REACTION UNDER SOLVENT-FREE AND MICROWAVE IRRADIATION CONDITIONS^a

Entry	Catalyst (mol %)	Time (min)	Yield (%) ^b
1	None	30	34
2	5	8	62
3	15	8	74
4	20	6	86
5	25	6	82
6	30	6	81

^a1 mmol 2-aminobenzamide and 2 mmol triethylorthoformate. ^bThe yields were calculated based on 2-aminobenzamide and refer to the pure isolated product


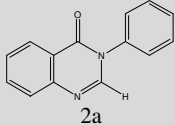

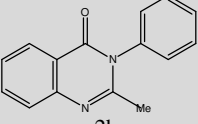

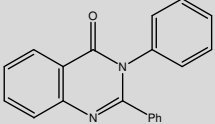
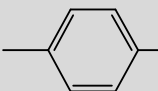
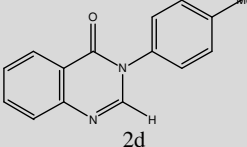

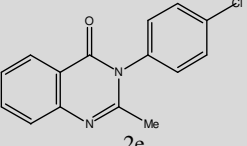

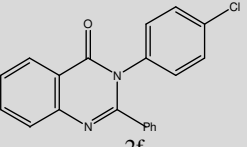
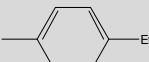
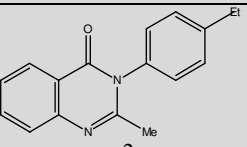

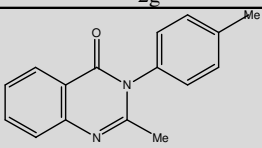

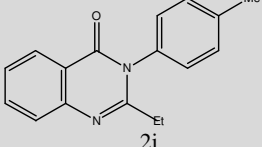
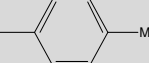
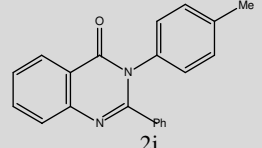
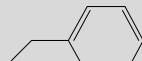
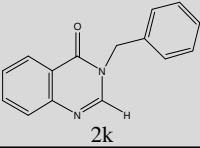
The effects of solvents such as acetone, dichloromethane, chloroform, acetonitrile, methanol and ethanol were also studied. According to Table-2, the yield of the reaction under solvent-free conditions was greater and the reaction time was generally shorter than the conventional methods. In order to evaluate the generality of this model reaction, we reported a range of 2,3-disubstituted quinazolin-4(3H)-ones **2a-2k** under optimized reactions in the presence of pentafluorophenylammonium triflate and microwave irradiation conditions. The results are shown in Table-3. Reusability of the catalyst was also investigated. After the completion of the reaction the catalyst was

TABLE-2
SYNTHESIS OF **2a** IN THE PRESENCE OF PENTAFLUOROPHENYLAMMONIUM TRIFLATE (20 mol %) IN THE DIFFERENT SOLVENTS UNDER MICROWAVE IRRADIATION CONDITIONS^a

Entry	Solvent	Time (min)	Yield (%) ^a
1	Acetone	45	60
2	Acetonitrile	45	78
3	Ethanol	45	74
4	Methanol	45	76
5	Dichloromethane	45	67
6	Chloroform	45	68
7	Solvent-free	6	86

^aIsolated yield

TABLE-3
REACTION OF DIFFERENT 2-AMINOENZAMIDES WITH TRIETHYLORTHOESTERS EMPLOYING PFPAT CATALYST^a

Entry	Ar	R	Product ^b	Yield ^c	m.p. (°C)	L. m.p. (°C) [ref]
1		H		86	138-139	139-141[18]
2		Me		84	145-146	146-147[25]
3		Ph		81	160-161	158-159[25]
4		H		86	144-145	145-148[18]
5		Me		82	154-156	155-156[25]
6		Ph		86	191-192	190-191[25]
7		Me		87	150-151	148-150[19]
8		Me		83	150-152	151-152[25]
9		Et		86	159-161	160-162[19]
10		Ph		84	181-183	180-181[18]
11		H		78	116-118	115-116[19]

^a1 mmol 2-aminobenzamide, 2 mmol triethylorthoformate and 0.2 mmol PFPAT. ^bAll the products were characterized by IR and ¹H NMR spectral data and comparison of their melting points with those of authentic samples. ^c Isolated yields based on 2-aminobenzamides

recovered according to the procedure mentioned in experimental section and reused for next reactions. The obtained results are summarized in Table-4. As shown in this table, the catalyst could be reused at least three times without appreciable reduction in the catalytic activity.

TABLE-4
COMPARISON OF EFFICIENCY OF PFPAT IN THE SYNTHESIS OF 2, 3-DISUBSTITUTED QUINAZOLIN-4(3H)-ONES AFTER THREE TIMES UNDER SOLVENT-FREE AND MICROWAVE IRRADIATION CONDITIONS

Run	First	Second	Third
Yield ^a (%)	86	84	81

^aIsolated yields

Conclusion

In conclusion we have successfully demonstrated the catalytic activity of pentafluorophenylammonium triflate in the synthesis of 2,3-disubstituted quinazolin-4(3H)-ones. The catalyst can be reused after a simple work-up, with a gradual decline for its activity being observed. Other advantages of this protocol are high yield, short reaction times, easy work-up and omitting any volatile and hazardous organic solvents.

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