Nafion-H: An Efficient and Recyclable Heterogeneous Catalyst for the One-Pot Synthesis of 2,3-Disubstituted 4-(3*H*)-Quinazolinones under Solvent-Free Microwave Irradiation Conditions

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Abstract: A one-pot synthesis of 2,3-disubstituted 4-(3*H*)-quinazolinones has been carried out efficiently by the three-component coupling of isatoic anhydride/anthranilic acid, orthoesters, and amines in the presence of Nafion-H (a perfluorinated resin-supported sulfonic acid) as a heterogeneous catalyst. The reaction occurred within a few minutes under solvent-free microwave irradiation conditions to afford the products in good yields. The catalyst was recovered and recycled.

Key words: quinazolin-4-(3*H*)-ones, Nafion-H, one-pot reaction, microwave irradiation

Multicomponent organic reactions using environmentally benign catalysts are of great interest in organic synthesis.[1] Today's environmental legislation demands clean and green reaction processes. Attempts have been made to develop green technologies with maximum yield and minimum cost whilst using non-toxic reagents, catalysts, and solvents, or even better, without solvents, which to some extent has been successful in a few transformations.[2] One of the tools to combine economic aspects with the environmental ones is the multicomponent reaction strategy; this process consists of three or more synthetic steps which are carried out without isolation of any intermediate, thus reducing time and saving energy and raw materials.[3] Catalysts play an important role in organic synthesis. The quest is always there for the development of eco-friendly and recyclable catalysts. As part of our programme aimed at developing new, selective, and environmentally friendly methodologies[4] for the preparation of fine chemicals, we wish to report herein the catalytic activity of Nafion-H for the one-pot synthesis of quinazolin-4-(3*H*)-ones.

Perfluorinated resin-supported sulfonic acid (Nafion-H)[5] has been extensively used as an eco-friendly catalyst in organic synthesis for alkylation,[6] acylation,[7] nitration,[8] acetal synthesis,[9] and in the Diels–Alder reaction.[10] The Nafion-H catalyst is an insoluble resin, inert to corrosive environments, stable up to 210 °C, easy to recover and recycle, which attracted our attention. The utility of this catalyst particularly depends on its relative inertness to corrosive environments and permselectivity, which preferentially allows cations to diffuse faster through the membranes than anions. Thus, Nafion-H was used as a catalyst for a multi-component condensation reaction for the first time and found to be an efficient catalyst to obtain 4-(3*H*)-quinazolinones in a single pot under microwave irradiation conditions.

Quinazolin-4-(3*H*)-one derivatives possess a broad spectrum of biological and pharmaceutical activities.[11] Several bioactive natural products contain the quinazolinone moiety,[12] such as febrifugine and isofebrifugine, naturally occurring 2-substituted 4-(3*H*)-quinazolinones, which exhibit high potential as anti-malarial compounds.[12,13] The synthesis of quinazolinone derivatives is achieved by cycloaddition reactions of anthranilic acid derivatives together with a diverse range of substrates including imidates and iminohalides.[14] However, some of these methods are associated with certain drawbacks such as a multi-step procedure, costly reagents, harsh reaction conditions, complex experimental process, long reaction times, and low yields. Thus, several previous methods have been excluded from practical application due to environmental and economic considerations. Therefore, there is still a need to develop appropriate efficient methods for the synthesis of 4-(3*H*)-quinazolinones.

In continuation of our efforts to explore the application of Nafion-H,[15] the solvent-free, three-component condensation of isatoic anhydride/anthranilic acid, orthoesters, and aromatic amines under microwave irradiation conditions were investigated. Accordingly, an equimolar mixture of isatoic anhydride, triethylorthoformate, and trifluoromethylaniline was subjected to microwave irradiation in the presence of Nafion-H and the progress of the reaction was monitored by TLC once a minute. After three minutes we observed the complete disappearance of starting materials. The reaction mixture was cooled, dissolved in ethyl acetate, and filtered to recover the catalyst. Concentration of the reaction mixture afforded quinazolin-4-(3*H*)-one in 82% yield (Scheme 1, Table 1).

Encouraged by this result a wide range of structurally varied amines **3**, orthoesters **2**, and isatoic anhydride **1** were reacted and the results are summarized in Table 1. In all cases, the three-component reaction proceeded rapidly to afford the corresponding quinazolin-4-(3*H*)-ones **4** in good yields (71–86%). Most importantly, anilines having an electron-donating group (methyl) gave a high yield

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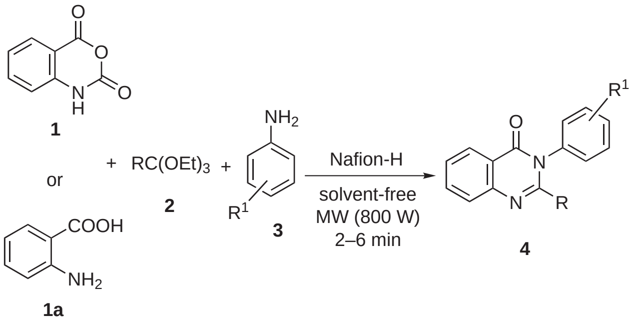
(89%) due to the increased electron density of the aromatic system, whereas electron-withdrawing groups (CF_3 and NO_2) gave a lower yield (71%). One more important observation is that anilines with a *meta* electron-withdrawing group gave a higher yield than those with a *para* electron-withdrawing group. Anilines containing two or more electron-withdrawing groups, resulted in a decrease in yield and prolonged reaction times compared to those with a single electron-withdrawing group. Substituents on the orthoester did not result in much variation in yield. When the same reaction was carried out using anthranilic acid instead of isatoic anhydride the yields were slightly higher, with a slightly shorter reaction time, and the substituent effect showed the same trend as earlier (Table 1).



Scheme 1

Table 1 Synthesis of 2,3-Disubstituted 4-(3*H*)-Quinazolinones[17]

Entry	R	R^1	Starting compd[a]	Time (min)	Yield[b] (%)	Mp (°C)
1	H	$3-CF_3$	I	3	82	135[16a]
			II	2	89	
2	H	$4-CF_3$	I	3	80	132[16b]
			II	2	86	
3	H	$2-Cl, 5-CF_3$	I	4	78	118[16c]
			II	3	84	
4	H	$2-NO_2, 4-CF_3$	I	5	77	176
			II	4	82	
5	H	$2,6-(NO_2)_2, 4-CF_3$	I	6	75	164
			II	4	80	
6	H	4-Me	I	3	89	147[16d]
			II	2	92	
7	Me	$3-CF_3$	I	3	88	140[16e]
			II	2	90	
8	Me	$4-CF_3$	I	3	78	146[16b]
			II	2	81	
9	Me	$2-Cl, 5-CF_3$	I	4	77	108[16e]
			II	3	82	
10	Me	$2-NO_2, 4-CF_3$	I	5	74	185
			II	4	78	
11	Me	$2,6-(NO_2)_2, 4-CF_3$	I	6	72	156
			II	4	75	
12	Me	4-Me	I	3	86	149[16f]
			II	2	94	
13	Et	$3-CF_3$	I	3	86	162
			II	2	88	
14	Et	$4-CF_3$	I	3	82	159
			II	2	87	
15	Et	$2-Cl, 5-CF_3$	I	4	76	104
			II	3	79	
16	Et	$2-NO_2, 4-CF_3$	I	5	73	167
			II	4	77	
17	Et	$2,6-(NO_2)_2, 4-CF_3$	I	6	70	186
			II	4	75	
18	Et	4-Me	I	3	83	162[16f]
			II	2	91	
19	Ph	$3-CF_3$	I	3	85	128
			II	2	89	
20	Ph	$4- CF_3$	I	3	83	122
			II	2	87	
21	Ph	$2-Cl, 5-CF_3$	I	4	77	206
			II	3	80	
22	Ph	$2-NO_2, 4-CF_3$	I	5	75	222
			II	4	79	
23	Ph	$2,6-(NO_2)_2, 4-CF_3$	I	6	71	246
			II	4	78	
24	Ph	4-Me	I	3	81	179[16f]
			II	2	92	

[a] I: isatoic anhydride; II: anthranilic acid.
[b] Isolated yields.

Encouraged by the results we concentrated on the recyclability of the Nafion-H catalyst. Accordingly, the recovered catalyst was reused using a model reaction of isatoic anhydride, triethyl orthoacetate, and 3-trifluoromethyl aniline under solvent-free microwave irradiation conditions. After completion of the reaction, ethyl acetate was added, and the mixture was filtered to separate the catalyst. The separated catalyst was used for further runs and did not show any reduced activity even after six runs (Table 2).

Table 2 Recycling of Nafion-H Catalyst

Run	Time (min)	Yield[a] (%)
1	3	88
2	3.5	86
3	4	85
4	4.5	86
5	6	88
6	6	86

[a] Isolated yield.

In conclusion, we have demonstrated that eco-friendly Nafion-H catalyst could be used efficiently for the synthesis of quinazolinones with good yields under solvent-free microwave irradiation conditions in short reaction times. The notable factors of this reaction are: (a) reasonably good yields; (b) solvent-free conditions; (c) choice of appropriate substituents on the aniline; (d) microwave irradiation conditions; (e) the catalyst Nafion-H can be easily recovered; (f) green synthesis avoiding toxic solvents; and (g) recyclability of the catalyst. Thus, we believe that, the developed procedure will find important practical applications for the synthesis of 4-(3*H*)-quinazolinones.

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(17) **General Procedure:** A mixture of isatoic anhydride (1.8 mmol) or anthranilic acid (1.8 mmol), triethyl orthoester (1.8 mmol), aromatic aniline (1.8 mmol), and a catalytic amount of Nafion-H was irradiated in a domestic microwave oven at 800 W in an open tube for 2–6 min. After completion of the reaction the reaction mixture was allowed to cool to ambient temperature, dissolved in EtOAc, and the catalyst was separated by filtration. The organic layer was dried with Na_2SO_4 and concentrated. The solid was passed through a silica gel column (*n*-hexane–$CHCl_3$, 1:1) to furnish the title compound in sufficiently pure form.