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1 2 3 X=O 4 X=S

R_1=H, 5-F or 4,5-dimethoxy X=O or S

R_2=substituted phenyl or alkyl

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Microwave-Assisted Efficient and Convenient Synthesis of 2,4(1*H*,3*H*)-Quinazolinediones and 2-Thioxoquinazolines

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An efficient and convenient method was developed for the preparation of 2,4(1*H*,3*H*)-quinazolinediones and 2-thioxoquinazolinones. Substituted methyl anthranilate reacted with various iso(thio)cyanates in DMSO/H_2O without any catalyst or base by using microwave irradiation to generate diversity on the 2,4(1*H*,3*H*)-quinazolinediones or 2-thioxoquinazolinones. A variety of substrates can participate in the process with good yields and high purities, making this methodology suitable for library synthesis in drug discovery efforts.

Introduction

The quinazolinone moiety is an important scaffold embedded in a variety of natural purine bases,[1] alkaloids, many biologically active compounds and intermediates in organic synthesis.[2] Quinazolineones are responsible for a variety of biological responses, including applications for hypertension,[3] diabetes,[4] cancer,[5] inflammation,[6] and immunosuppression.[6]

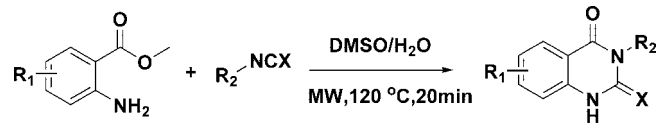
As a consequence, much attention has been paid to the development of efficient methods for preparation of substituted 2,4(1*H*,3*H*)-quinazolinediones or 2-thioxoquinazolinones. Most typical methods need long reaction times, multiple steps, or both.[7] Garin et al.[8] and Calestani et al.[9] reported the synthesis of 2,4-quinazolinediones involving metal-catalyzed reactions, but the use of HgO or $Mn(OAc)_3$ is less than ideal because of their negative environmental impact; Lewis acid $AlCl_3$[10] catalyzed reactions gave unsatisfactory yields accompanied by significant byproducts. Choo[5] developed a solid-phase combinatorial synthesis of 3-aryl-2,4-quinazolinediones, but the overall yields were low (2%−60%) because of the large number of reaction steps. Recently, Willis[11] and co-workers reported the Pd-catalyzed regioselective synthesis of 3-alkylated 2,4-quinazolinediones; however in addition to requiring special catalyst and ligand, their methodology is still limited by long reaction times. Therefore, a method with higher yields, cheaper reagents, and more convenient manipulation needs to be developed.

Microwave (MW) irradiation has been widely applied in organic synthesis, including aromatic nucleophilic substitution, cycloaddition, and organometallic reactions.[12] It accelerates a variety of synthetic transformations via time- and energy-saving protocols.[12] Although the microwave-assisted synthesis of 2-thioxoquinazolinones was previously developed by Javad Azizan,[13] the diversity of products was limited because of the use of isatoic anhydride as a starting material.[13] In this work, we report a novel and convenient MW-assisted protocol for the synthesis of 2,4(1*H*,3*H*)-quinazolinediones and 2-thioxoquinazolineones in one pot using commercially available substituted methyl anthranilate and various iso(thio)cyanates with the idea of combinatorial chemistry (Scheme 1).

Our process is characterized by (i) faster reaction times and generally good to excellent yields, (ii) the use of DMSO/H_2O as solvent without any catalyst, base, or ligand, and (iii) isolation of products via simple precipitation and filtration to give higher purities.

Initially we studied the MW-assisted synthesis of quinazolinediones using methyl anthranilate and 2-(trifluoromethyl)phenyl isocyanate as model substrates. The reaction conditions were optimized by testing several parameters, such as various solvents, different temperatures, and different reaction times. The results are summarized in Table 1. No expected compound was detected when THF or dioxane was used as solvent (entries 1−4, Table 1). Compound **5**, the product of CO-extruding isocyanate dimerization,[14] was

Scheme 1. Microwave-Assisted Synthesis of 2,4(1*H*,3*H*)-Quinazolinediones and 2-Thioxoquinazolinones



1 2 3 X=O 4 X=S

R_1=H, 5-F or 4,5-dimethoxy X=O or S

R_2=substituted phenyl or alkyl

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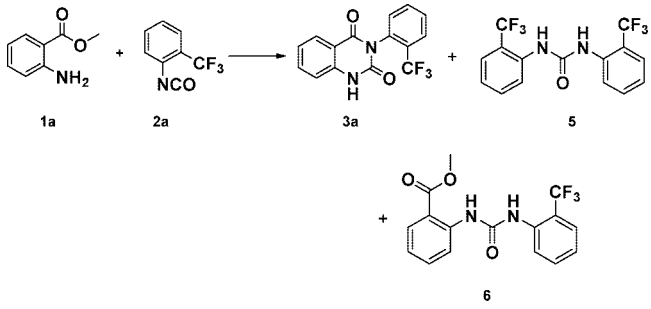
Table 1. Optimization for the Microwave-assisted Reaction[a]



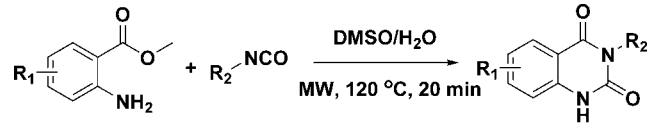
				yields[c] (%)		
entry	solvent	temp (°C)	time (min)	**3a**	**5**	**6**
1	THF + TEA	60	10		52	
2	THF	90	10	0		67
3	THF	120	10	13		54
4	dioxane	120	10	0		27
5	DMF	120	10	10[d]		22[d]
6	DMSO	120	10	5[d]		37[d]
7	THF/H_2O[b]	120	10	35		41
8	DMF/H_2O[b]	120	10	33		26
9	dioxane/H_2O[b]	120	10	47		16
10	DMSO/H_2O[b]	120	10	68		19
11	DMSO/H_2O[b]	120	15	75		16
12	DMSO/H_2O[b]	120	20	88		5
13	DMSO/H_2O[b]	140	20	79		7
14	DMSO/H_2O[b]	120	300	43		29

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), DMSO (1.5 mL), H_2O (1.5 mL), MW. [b] V_{sol}/V_{water} = 1/1. [c] Isolated yields. [d] Yields determined by LC-MS without isolation.

formed as the main product in THF with additional 1.0 equiv of TEA (entry 1, Table 1). Urea **6** was identified as the main product when the temperature was increased to 90 °C (entry 2, Table 1), indicating that the condensative cyclization required higher reaction temperatures.[15] Only trace expected product was obtained when DMF or DMSO was used as solvent at 120 °C (entries 5 and 6, Table 1). It was thought that the cyclization may require nucleophilic solvent, such as H_2O, to facilitate the elimination of methanol. Solvent effects revealed that a mixture of DMSO and water was superior to other solvents (entries 7−10, Table 1). Prolonging the reaction time led to a significant improvement in reaction yields (entries 10−12, Table 1). No gain was observed when the temperature was further increased (entry 13, Table 1). Finally, a general condition without microwave was adopted to compare the difference between the two methods (entry 14, Table 1), and the superiority of microwave was observed distinctly.

With the optimized conditions in hand, we then examined the generality of the process. As shown in Table 2, we were pleased to find that the method was applicable to a broad substrate scope on both substituted methyl anthranilates and isocyanates. The results indicated that the aryl isocyanates were well tolerated (entries 1−9, Table 2), while the aliphatic isocyanates typically gave lower yields (entries 11 and 12, Table 2). Aryl isocyanates containing various electron-donating and electron-withdrawing substituents were reacted under the optimized conditions, and the corresponding products were obtained in good to excellent yields (entries 1−9 and 13−17, Table 2). No remarkable electronic effects on the reaction was observed. Reactions of aryl isocyanates substituted with electron-withdrawing groups (entries 1−4, Table 2) and electron-donating groups all proceeded in high yields (entries 5−8, Table

Table 2. Microwave-Assisted Synthesis of 2,4(1*H*,3*H*)-Quinazolinediones



1 2 3

entry	R_1	R_2	products	yields (%)[a]
1	H	2-$F_3CC_6H_4$	**3a**	86
2	H	3-$F_3CC_6H_4$	**3b**	92
3	H	4-$F_3CC_6H_4$	**3c**	90
4	H	4-FC_6H_4	**3d**	81
5	H	2-$MeOC_6H_4$	**3e**	83
6	H	3-$MeOC_6H_4$	**3f**	79
7	H	4-$MeOC_6H_4$	**3g**	80
8	H	4-MeC_6H_4	**3h**	70
9	H	4-BrC_6H_4	**3i**	73
10	H	2,6-di-*i*-PrC_6H_4	**3j**	0
11	H	cyclohexy	**3k**	24
12	H	octyl	**3l**	23
13	5-F	2-$MeOC_6H_4$	**3m**	56
14	5-F	3-$MeOC_6H_4$	**3n**	70
15	5-F	4-$MeOC_6H_4$	**3o**	56
16	5-F	3-$F_3CC_6H_4$	**3p**	61
17	5-F	4-$F_3CC_6H_4$	**3q**	79

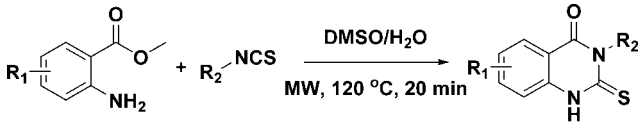
[a] Isolated yield.

2), while the former were obtained with a little higher yields than the latter, which may be consistent with the view that the π-electron system of the phenyl ring of the isocyanates reduces the electron density on the carbon atom of the $-N{=}C{=}O$ moeity, enhancing its reactivity, while electron-withdrawing substituents further strengthen the effect. No significant steric effects were observed for the ortho-, meta-, and para-substituted aryl isocyanates (entries 1−3 and 5−7, Table 2). However, the cyclization was impeded by severe steric hindrance. For example, no desired product was obtained when 2,6-di-*i*-Pr-substituted aryl isocyanate was used (entry 10, Table 2). The yields of aliphatic isocyanates still needs to be improved (entries 11−12, Table 2). The effects of substituted methyl anthranilate were also investigated. Fluorine substitution reduces the nucleophilicity of the amine, giving moderate to good yields (entries 13−17, Table 2) compared with nonsubstituted methyl anthranilate (entries 2−3 and 5−7, Table 2).

Encouraged by these results, we next focused our attention on the synthesis of 2-thioxoquinazolinones under optimized conditions. The desired product **4a** was obtained with a yield of 73% by reaction of methyl anthranilate with phenyl isothiocyanate. The IR spectra of **4a** showed intense peaks at 3220 cm^{-1} for cyclic thiourea (NH), 1660 cm^{-1} for carbonyl (C═O), and 1200 cm^{-1} for thioxo (C═S) stretching. ^{1}H NMR spectra of **4a** showed a multiplet at δ 7.0−9.0 for the aromatic (9H) protons.[2] Compared with isocyanates, isothiocyanates showed similar reactivity trends. The yields of aryl-substituted isocyanates were superior to those of aliphatic ones (entries 1−10 and 11−12, Table 3). Meanwhile it was found that the yields of isothiocyanates were a little lower than that of isocyanates, which may be a result of the weaker electronegativity of sulfur compared with oxygen. Good or moderate yields were also obtained when 5-F or 4,5-dimethoxy-substituted methyl anthranilate reacted with isothiocyanates (entries 13−18, Table 3).

In conclusion, we have developed an efficient and convenient method for the preparation of 2,4(1*H*,3*H*)-quinazo-

Table 3. Microwave-Assisted Synthesis of 2-Thioxoquinazolin-ones



1 2 4

entry	R_1	R_2	products	yields (%)[a]
1	H	C_6H_5	**4a**	73
2	H	2-$MeOC_6H_4$	**4b**	50
3	H	3-$MeOC_6H_4$	**4c**	70
4	H	4-$MeOC_6H_4$	**4d**	70
5	H	2-MeC_6H_4	**4e**	66
6	H	3-MeC_6H_4	**4f**	70
7	H	2-BrC_6H_4	**4g**	70
8	H	3-ClC_6H_4	**4h**	57
9	H	3-$F_3CC_6H_4$	**4i**	87
10	H	4-$F_3CC_6H_4$	**4j**	90
11	H	ethyl	**4k**	34
12	H	butyl	**4l**	13
13	5-F	C_6H_5	**4m**	67
14	5-F	2-$MeOC_6H_4$	**4n**	64
15	5-F	3-$MeOC_6H_4$	**4o**	86
16	5-F	2-$F_3CC_6H_4$	**4p**	80
17	5-F	4-$F_3CC_6H_4$	**4q**	87
18	4,5-dimethoxy	C_6H_5	**4r**	60

[a] Isolated yield.

linediones and 2-thioxoquinazolinones. The process was carried out in DMSO/H_2O without any catalyst or base by using microwave irradiation to generate diversity on the quinazolineones. A variety of substrates can participate in the process with good yields. The procedure used commercially available substituted methyl anthranilate and substituted iso(thio)cyanates and is suitable for library synthesis in drug discovery efforts. In particular, after the reaction mixtures were cooled to ambient temperature, a large amount of desired products precipitated and could easily be collected by filtration with higher purities. The short reaction times and simple reaction conditions render this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

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Supporting Information Available. Reaction procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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