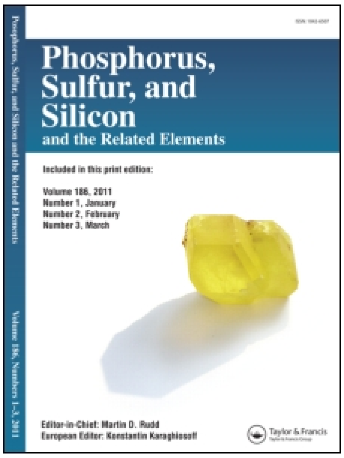

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A CONVENIENT SYNTHESIS OF SUBSTITUTED QUINAZOLIN-4(3H)-ONES UNDER MICROWAVE AND SOLVENT-FREE CONDITIONS

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A clean and facile synthesis of the title compounds is achieved from cyclocondensation of 2-aminobenzamides with orthoesters catalyzed by SiO_2/H_2SO_4 *in dry and microwave conditions.*

Keywords: Microwave; quinazolin-4(3H)-ones; solvent-free; sulfuric acid on silica

Natural and synthetic compounds with quinazoline structural motif have been identified to display a wide range of biological activities. The prominent potencies associated with quinazoline containing compounds are their anti-inflamatory,[1] anthelmintic,[2] analgesic,[3] CNS depressant,[4] anticancer,[5] and anticonvulsive[6] activities. Because of these widespread activities, their synthesis was continually the subject of much research[7] and is still pursued due to new emerging methods, such as microwave heating.[8] Performing reactions under microwave irradiation frequently gives rise to some rate enhancement and improvement of yields. Microwave condition is best suited to the so-called solvent-free reactions. These reactions are eco-friendly and, in view of green chemistry's desire to avoid solvent hazards, are in demand.

As a finding of our ongoing research projects on the synthesis of quinazoline derivatives,[9] we now report that microwave-assisted cyclocondensation of 2-aminobenzamides **1** with orthoesters **2** on silica-supported sulfuric acid quickly provides the substituted quinazolin-4(3H)-ones **3** in fairly high yields. To our knowledge, there has been no

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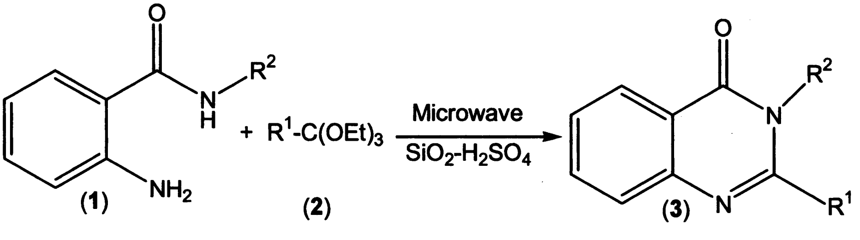
report on the use of sulfuric acid adsorbed on silica gel (SiO_2/H_2SO_4) as a solid catalyst in the synthesis of quinazolines (Scheme 1).



SCHEME 1

The early method, based on the reaction of 2-aminobenzamide with orthoester, was performed in the presence of H_2SO_4, and as a requirement of its refluxing condition much excess of orthoester was used.[10] Although an excess of orthoester is necessary to diminish the intermolecular side reactions, the conventional heating method needs additional orthoester both to act in place of solvent and to improve the yield. In contrast to the liquid H_2SO_4, which is difficult to recover and takes some effort in workup, the silica-supported H_2SO_4 can be easily separated and recycled without the loss of activity for several times. Thus, 2-aminobenzamides **1** reacted with nearly 2 equivalents of orthoesters **2** with the aide of $SiO_2/H_2SO_4$and submission to microwave irradiation to provide fairly high yields of substituted quinazolin-4(3H)-ones **3a–i** in a few minutes (Table I). At the same time, in the absence of catalyst

TABLE I Physical Data of the Compounds **3a–3i**

Product	R^2	R^1	Yield (%)[f]	m.p. (°C)	Lit. m.p. (°C)
3a	Ph	H	84	137–138	137–138[a]
3b	Ph	CH_3	85	146–147	147–148[b]
3c	Ph	Ph	92	158–159	158[c]
3d	4-MeC_6H_4	H	88	144–145	143–144[a]
3e	4-MeC_6H_4	CH_3	90	151–152	151–152[b]
3f	4-MeC_6H_4	Ph	95	180–181	180–181[c]
3g	4-ClC_6H_4	H	87	180–181	180–181[a]
3h	4-ClC_6H_4	CH_3	92	155–156	157–158[d]
3i	4-ClC_6H_4	Ph	97	190–191	189–190[e]

[a] Runti et al.[11]
[b] Errede et al.[12]
[c] Levy and Stephen.[13]
[d] Grimmel et al.[14]
[e] Petyunin et al.[15]
[f] Yields of separated products, based on 2-aminobenzamides, **2**.

or by mixing the catalyst with reactants without exposure to microwave irradiation, no reaction took place.

In conclusion, in comparison with the previous related methods[10,16] which show drawbacks from the standpoints of prolonged refluxing in solvent, need for inert gas, and consuming more orthoester, the notable advantages of this methodology are: mild conditions in a solvent-free system, fairly high yields, fast reaction, no aqueous workup, and safe and environmental friendly conditions.

EXPERIMENTAL

All products were known compounds and identified by comparison with authentic samples. The catalyst is prepared by mixing chromatographic-grade silica (Merck, Darmstadt, Germany, Kiesel gel, 60, 70–230 mesh) with 3% of its weight of sulfuric acid dissolved in acetone following a reported method.[17] 2-Aminobenzamides **1** were prepared according to a reported procedure from the readily available isatoic anhydride and the proper primary amine.[18] Melting points were measured on a Mettler FP5 electrothermal apparatus and are uncorrected. Microwave irradiations were carried out in a 700 W domestic microwave oven at 2450 MHz. In order to control the reaction violence, irradiations were performed in two stages with a cooling time between them.

General Procedure

A mixture of **1** (0.005 mole), orthoester **2** (2 ml in each case), and 0.2 g of finely ground silica-supported sulfuric acid was placed in a 100 ml beaker. The beaker was covered with a stemless funnel and then irradiated in the microwave oven for 2 min with power of 120 W. After a cooling time of about 3 min to room temperature, the beaker was irradiated again for 3 min at 120 W. After completion of the reaction (monitored by thin layer chromatography (TLC) using ethyl acetate: hexane 1:1) the hot residue was dissolved in 8 ml of ethanol 95%. 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%.

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