Silica-supported Sodium Hydrogen Sulfate and Amberlyst-15 : Two Efficient Heterogeneous Catalysts for Single-step Synthesis of 4(3*H*)-Quinazolinones from Anthranilic Acid, Ortho Esters, and Amines under Solvent Free Conditions

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(Received May 6, 2004; CL-040510)

The single step synthesis of 4(3*H*)-quinazolinones has been carried out efficiently by coupling of the three components, anthranilic acid, ortho esters, and amines in the presence of silica-supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) or Amberlyst-15 as a heterogeneous catalyst. The reaction occurred within a few minutes under solvent free conditions to afford the products in excellent yields. One of the catalysts, Amberlyst-15 can be recovered and recycled.

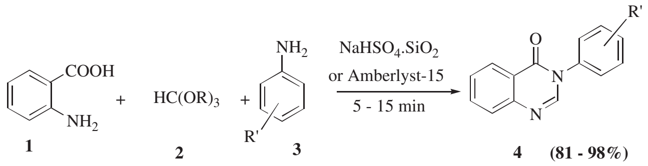
4(3*H*)-Quinazolinones are a class of fused heterocycles that are of significant importance because of the broad spectrum of their biological properties such as anticancer, anticonvulsant, antihypertensive, antiinflamatory, and antimalerial activities.[1] Several bioactive natural products contain quinazolinone moiety.[2] As for an example, febrifugine and isofebrifugine, which are naturally occurring 2-substituted 4(3*H*)-quinazolinones, are highly potential antimalerial compounds.[2,3] The synthesis of quinazolinone derivatives is achieved by cyclo-addition reactions of anthranilic acid derivatives together with a diverse range of substrates including imidates and iminohalides.[4] However, some of these methods are associated with certain drawbacks such as multi-step procedure, costly reagents, harsh reaction conditions, complex experimental process, long reaction times, and low yields. The catalysts which were used earlier work mostly under homogeneous conditions and so the recovery of these catalysts is always a problem. Thus several previous methods have been excluded from practical applications due to environmental and economic considerations. Therefore, still there is need to develop appropriate efficient methods for the synthesis of 4(3*H*)-quinazolinones.

Multicomponent reactions are recently of practical importance due to their speed, diversty, and efficiency. We have developed an expeditious one-pot synthesis of 4(3*H*)-quinazolinones (**4**) from the reaction of three components, anthranilic acid (**1**), orthoesters (**2**) and anilines (**3**) in the presence of a heterogeneous catalyst, silica-supported sodium hydrogen sulphate ($NaHSO_4 \cdot SiO_2$) or Amberlyst-15.[5] Various 4(3*H*)-quinazolinones (**4**) were prepared (Table 1) using different substitued anilines (**3**) and trimethyl or triethyl orthoformate (**2**). The reaction was carried out under solvent free conditions. The products (**4**) were formed within a few minutes in excellent yields. Most of the reactions proceeded at room temperature but when an aniline contains a nitro group the reaction mixture was refluxed at 60 °C and the times required were somewhat more (15 min). For 2,5-dimethoxyaniline also heating of the mixture for 10 min was necessary. This may be due to the steric reason. The products derived from aniline containing electron donating groups were formed in somewhat higher yields than those from anilines having electron withdrawing groups. The reaction could tolerate different functionalities, e.g., alkyl, halogen, ether, and nitro present in the anilines. Trimethyl and triethyl orthoformates reacted almost similarly.

Table 1. Preparation of 4(3*H*)-quinazolinones (4a - 4r) catalyzed by $NaHSO_4 \cdot SiO_2$ and Amberlyst-15[a]

Entry	R	R′	Catalyst[b]	Time /min.	Isolated Yield /%
a.	Me	H	I	5	94
			II	5	96
b.	Me	4-Me	I	5	93
			II	5	97
c.	Me	4-OMe	I	5	95
			II	5	98
d.	Me	2-Cl	I	10	88
			II	10	90
e.	Me	3-Cl	I	10	91
			II	10	92
f.	Me	4-F	I	10	87
			II	10	90
g.	Me	$2\text{-}NO_2$	I	15	81
			II	15	82
h.	Et	H	I	5	91
			II	5	92
i.	Et	4-Me	I	5	94
			II	5	96
j.	Et	4-OMe	I	5	95
			II	5	98
k.	Et	2-Cl	I	10	89
			II	10	92
l.	Et	3-Cl	I	10	91
			II	10	93
m.	Et	4-F	I	10	85
			II	10	86
n.	Et	$2\text{-}NO_2$	I	15	81
			II	15	82
o.	Et	$4\text{-}NO_2$	I	15	83
			II	15	85
p.	Et	2,5-di(OMe)	I	10	84
			II	10	86
q.	Et	2,6-di(Me)	I	10	81
			II	10	85
r.	Et	4-Br	I	5	89
			II	5	90

[a] The structures of the products were settled from their ^1H NMR and MS data.
[b] Catalyst I : $NaHSO_4 \cdot SiO_2$; II : Amberlyst-15



1 2 3 4 (81 - 98%)

The catalysts, $NaHSO_4 \cdot SiO_2$ and Amberlyst-15 work under heterogeneous conditions. In recent years heterogeneous catalysts have attracted more attention as they catalyze the chemical processes under eco-friendly manner and with satisfactory yields and low cost. Both the presently used catalysts can conveniently be handled and removed from the reaction mixture after completion of the reaction. $NaHSO_4 \cdot SiO_2$ can be prepared[6] easily from the readily available ingredients, $NaHSO_4$ and silica gel. The activity and efficiency of both the catalysts for the present conversion are comparable. However, Amberlyst-15 can be recovered, activated and recycled.

In conclusion, we have developed a simple and efficient three-component coupling reaction of anthranilic acid, orthoesters, and amines using $NaHSO_4 \cdot SiO_2$ or Amberlyst-15 for the preparation of 4(3*H*)-quinazolinones in single step. The mild and solvent free heterogeneous reaction conditions, short reaction times (5–15 min), simple experimental procedure, excellent yields (81–98%) and reusability of one of the catalysts (Amberlyst-15) are of great advantages of the present protocol. The process is associated with the combined benefits derived from multicomponent reaction and heterogeneous catalyst. We feel that the developed procedure will find important practical applications for the synthesis of 4(3*H*)-quinazolinones.

The authors thank CSIR, New Delhi for financial assistance.

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5 General experimental procedure: To a mixture of anthranilic acid (1 mmol), an orthoester (1.2 mmol), and an amine (1.2 mmol) $NaHSO_4 \cdot SiO_2$ (100 mg, the ratio of $NaHSO_4$ and SiO_2 was 2:5) or Amberlyst-15 (50 mg) was added. The mixture was stirred at room temperature. The reaction was monitored by TLC. After completion CH_2Cl_2 (10 mL) was added to the reaction mixture and filtered. The filtrate was washed with aq HCl (5%) (3×5 mL) and subsequently with H_2O (3×10 mL). The organic layer was dried and the solvent was evaporated to get 4(3*H*)-quinazolinone. When the reaction was carried out with a nitroaniline or with 2,5-dimethoxyaniline the reaction mixture was refluxed at 60 °C. Amberlyst-15 was recovered from the residue of filtration of the reaction mixture by washing throughly with CH_2Cl_2, activated and recycled. The efficiency of the recovered Amberlyst-15 was verified with the reaction of anthranilic acid, trimethyl orthoformate and aniline (Entry a). Using the fresh catalyst the yield of the product, 3-phenyl-4(3*H*)-quinazolinone (**4a**) was 94% while with the recovered catalyst in the three subsequent recyclization the yields were 92, 89, and 88%. The spectral properties of some representative 4(3*H*)-quinazolinones are given below.: **3-Phenyl-4(3*H*)-quinazolinone (4a)**, ^1H NMR ($CDCl_3$, 200 MHz): *d* 8.68 (1H, d, $J = 8.0$ Hz), 8.31 (1H, s), 7.52 (2H, d, $J = 8.0$ Hz), 7.38–7.22 (5H, m), 7.16 (1H, m); EIMS: m/z (%) 222 (M^+, 5), 221 ($M^+ - 1$, 4) 121 (92), 93 (100). **3-(3-Chlorophenyl)-4(3*H*)-quinazolinone (4e)**, ^1H NMR ($CDCl_3$, 200 MHz): *d* 8.32 (1H, d, $J = 8.0$ Hz), 8.12 (1H, s), 7.89–7.61 (2H, m), 7.61–7.53 (4H, m), 7.40 (1H, m); EIMS: m/z (%) 257 ($M^+ + 1$, 22), 256 (M^+, 23), 221 (12), 149 (78), 111 (22). **3-(2,6-Dimethyl phenyl)-4(3*H*)-quinazolinone (4q)**, ^1H NMR ($CDCl_3$, 200 MHz): *d* 8.38 (1H, d, $J = 8.0$ Hz), 7.88–7.72 (2H, m), 7.55 (1H, t, $J = 8.0$ Hz), 7.36–7.20 (3H, m), 7.02 (1H, m), 2.18 (6H, s); EIMS: m/z (%) 250 (M^+, 62), 233 (91), 149 (46), 125 (12), 103 (38).

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Published on the web (Advance View) June 28, 2004; DOI 10.1246/cl.2004.960