Eco-Friendly, Solvent-Free Novel One-Pot, Three-Component Synthesis of Quinazolinones at Ambient Temperature Catalyzed by Silica Gel-Supported Phosphomolybdic Acid

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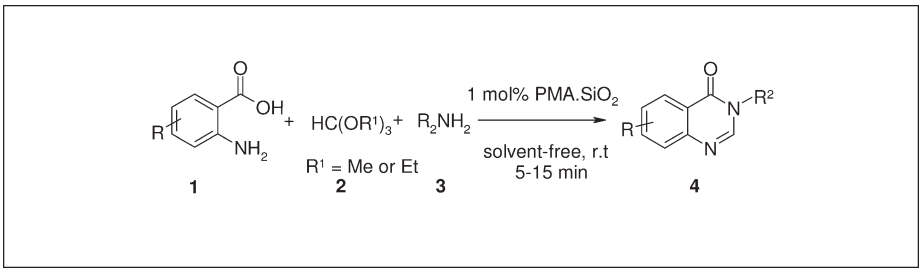

Silica gel supported Phosphomolybdic acid ($PMA.SiO_2$) catalyzes efficiently the one-pot three-component coupling reaction of anthranilic acid, orthoesters, and amines at room temperature to afford 4(3*H*)-Quinazolinones in high to excellent yields under solvent-free conditions. The supported catalyst can be recovered and reused.

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INTRODUCTION

The demand for increasingly clean and efficient chemical syntheses is continuously becoming more urgent from both an economic and an environmental standpoint. Organic reactions under solvent-free conditions are advantageous because of enhanced selectivity and efficiency, ease of manipulation, and more importantly, toxic and often volatile solvents are avoided. These would be especially important during industrial production. Hence, the organic transformations under solvent-free conditions are attracting increasing attention.

Heteropoly acids are economically and eco-friendly green Lewis acids. Development of methods using heteropoly acids (HPAs) as catalysts for organic synthetic processes related to fine chemicals, such as flavors, pharmaceuticals, and food industries [1–4] have been under attention in the last decade. Heteropolyacids are more active catalysts than conventional inorganic and organic acids for various reactions in solution [5–11]. They are used as industrial catalysts for several liquid-phase reactions[12–15], such as alcohol dehydration [16], alkylation [17], or esterification [18] reactions. They are not corrosive and environmentally benign, presenting fewer disposal problems. Phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) belongs to the class of heteropoly acids. The supported HPAs are more active than typical solid acids and attracted much attention in organic synthesis owing to easy workup procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of the catalysts [19]. Supported reagents enhance their application in 'green synthesis'. Silica gel [17] is most commonly used as support, even though alumina, active carbon, and acidic ion-exchange resins are considered as suitable supports.

Natural products containing quinazolinone moiety possess a broad spectrum of biological properties, such as anticancer, antimalarial, anticonvulsant, analgesic, antihypertensive, antiviral, anti-tubercular, and anti-inflammatory activities [20–34]. Febrifugine and isofebrifugine natural products [35,36] containing 4(3*H*)quinazolinone scaffold have been used effectively against malarial fever in china for centuries (Fig. 1). Similarly, quinazolone containing compounds have been known as tyrosine kinase inhibitors [37,38], dihydrofolate reductase inhibitors [39], and tubulin polymerization inhibitors [40,41]. The interest in the quinazolone structural motif, led to a number of different synthetic methods to access this nucleus. The synthesis of 4(3*H*)-quinazolinone derivatives is achieved by cycloaddition reactions of anthranilic acid with imidates and imino halides [42–49]. The cyclization of cyano- and nitro- activated *o*-fluorobenzaldehydes with amidines and more recently, the

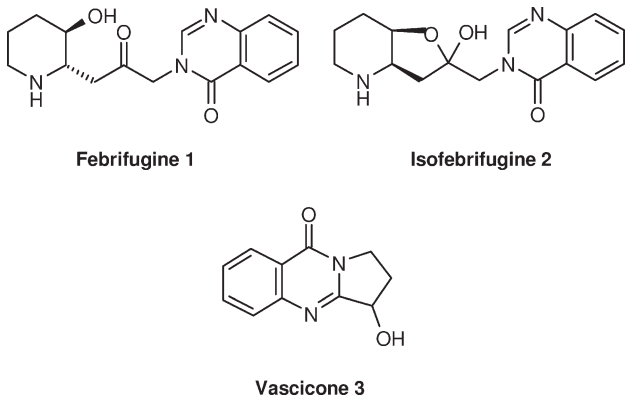


Figure 1. Quinazolinone moiety containing natural products.

condensation of fluoro substituted benzoyl chlorides with 2-amino-*N*-heterocycles represent one-pot approaches to quinazolines [50,51]. An intramolecular aza-Wittig type transformation of *o*-azidobenzamide derivatives has been employed as the key quinazolinone-forming step in the synthesis of the quinazoline alkaloid vasicinone [52]. Usually, 4*H*-3,1-benzaxazin-4-ones are valuable starting materials for the synthesis of these compounds [53]. Recently, 4(3*H*)-quinazolinones were prepared using $Bi(TFA)_3$-[nbp]$FeCl_4$ [54], $Yb(OTf)_3$ [55], $La(NO_3)_3.6H_2O$ [56], Silicagel/$FeCl_3$ [57], Silicagel/$NaHCO_3$ & Amberlist 15 [58]. Even-though, many reports appeared in the literature, some of these suffer from drawbacks, such as multi-step procedures, long reaction time, expensive reagents, low yields, harsh conditions, and cumber some product isolation.

As part of our program aimed at developing new green synthetic methodologies for the preparation of fine chemicals, we wish to report herein a remarkable catalytic activity of PMA for the one-pot synthesis of 4(3*H*)-quinazolinones.

RESULTS AND DISCUSSIONS

Thus carrying out the reaction of anthranilic acid **1** with trimethyl/ethyl orthoformate **2** and primary amine **3** in1:1.2:1.2 mole ratio in the presence of 1 mol % of PMA.SiO_2 [59] at room temperature gave the desired 4(3*H*)-quinazolinone **4** in 98% yield (Scheme 1). The experimental procedure is simple and the reaction proceeds under solvent-free conditions. To expand the scope of this method, various 4(3*H*)-quinazolinones were synthesized under similar conditions in high to excellent yields. All the reactions proceeded efficiently at room temperature within 5–15 min in excellent yields under solvent-free conditions and all the products were characterized by NMR, IR and mass spectroscopy and also by comparison with authentic samples. As shown in Table 1, both aniline derivatives and benzyl amine reacted similarly under these reaction conditions without any difference to give the corresponding 4(3*H*)-quinazolinones in high yields. The present procedure does not require toxic or anhydrous organic solvents. The reaction is general, clean, rapid, and efficient. It is important to note that in the absence of catalyst the reaction did not yield the products and only the starting materials were isolated.

It is important to mention that in contrast to reported procedures, *m*-nitroaniline reacted at room temperature with anthranilic acid and trimethyl orthoformate to produce the product **4j** in 88% yield within 15 min, while many of the reports claim the reaction using aniline containing a nitro group requires heating at 60°C [54,56–58]. The one-pot reaction proceeded smoothly with the anilines containing electron-donating groups (such as methoxy and methyl) as well as containing electron-withdrawing groups (such as chloro, fluoro, and nitro).

In conclusion, we have demonstrated a three-component, one-pot procedure for the synthesis of 4(3*H*)-quinazolinones at ambient temperature using silica gel supported PMA. The noteworthy advantages of this method are mild solvent-free heterogeneous reaction conditions, improved yields, shorter reaction times, and operational simplicity, which make it a useful and attractive process for the synthesis of 4(3*H*)-quinazolinones. The supported catalyst can be recovered and reused.

EXPERIMENTAL

All reactions were carried out under N_2 atmosphere and monitored by TLC on silica gel (60–120 mesh; Merck). IR spectra were recorded on a Thermo Nicolet Nexus-670 spectrometer; in *m*/*z*. ^{1}H NMR spectra were recorded on Bruker (300/75 MHz) spectrometer in $CDCl_3$; δ in ppm, *J* in Hz. ESI Mass spectra were recorded on Agilent LC-MSD-Trap-SL apparatus; in *m*/*z*.

General procedure for the preparation of Compound 4a. To a mixture of anthranilic acid **1** (1 mmol), trimethyl or triethyl orthoformate **2** (1.2 mmol) and aniline **3a** (1.2 mmol), silicagel supported PMA [59] (0.01 mmol) was added. The reaction mixture was stirred at room temperature for 5 min. After completion of the reaction (monitored by TLC) 10 mL of CH_2Cl_2 was added to the reaction mixture and the catalyst

Scheme 1

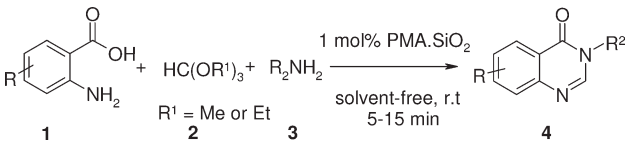
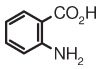
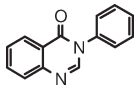
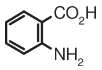
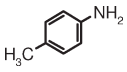
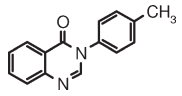
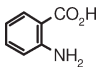
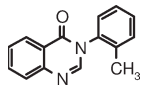
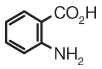
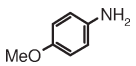
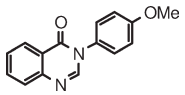
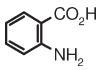
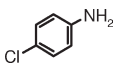
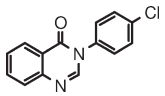
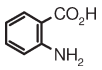
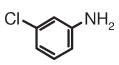
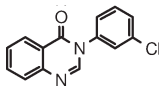
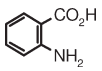
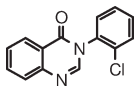
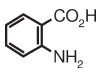
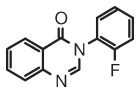
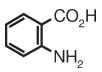
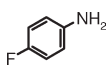
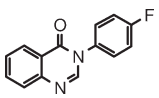
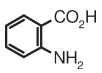
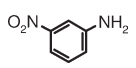
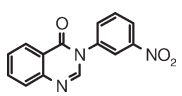
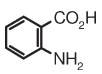
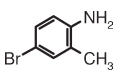
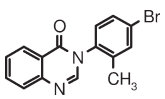
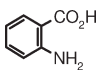
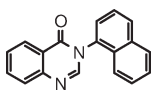
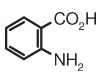
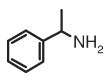
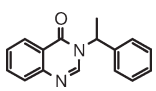
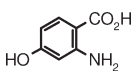


Table 1

PMA.SiO_2 catalyzed one-pot synthesis of 4(3*H*)-quinazolinones[a] at room temperature.

Entry	Anthranilic acid	Amine	Quinazolinone	Time (min)	Yield (%)[b]
a				5	98
b				5	98
c				5	96
d				5	95
e				8	95
f				8	94
g				8	94
h				10	92
i				10	92
j				15	88
k				8	95
l				8	90
m				5	91
n				8	95
o				10	92
p				10	92
q				6	94

[a] All products are characterized by NMR and Mass spectra.
[b] Yields refer to isolated pure products.

was recovered by filtration. The filtrate was washed with aq HCl (5%) (2 × 10 mL) followed by H_2O (2 × 5 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to get the crude product. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate 5:1 as eluent) to afford the pure product **4a** in 98% yield.

Selected spectroscopic data. ***Compound 4a.*** ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, 1H, J = 10.9 Hz), 8.36 (s, 1H), 7. 49 (d, 1H, J = 8.0 Hz), 7.39–7.23 (m,3H), 7.21–7.04 (m, 4H). IR (KBr): 1682, 1600, 1442, 1310, 753, 693 cm^{-1}. EIMS: *m*/*z* 223 (M^++1).

Compound 4b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, 1H, J = 11.3 Hz), 8.31 (s, 1H), 7.41–7.35 (m, 1H), 7.15–7.05 (m, 2H), 7.00–6.95 (m, 3H), 2.32 (s, 3H). IR (KBr):1686, 1607, 1518, 1297, 815 cm^{-1}. EIMS: *m*/*z* 237 (M^++1).

Compound 4m. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31(d, 1H, J = 8.0 Hz), 7.8 (s, 1H), 7.75–7.67 (m, 2H), 7.52–7.44 (m, 1H), 7.41–7.32 (m, 5H), 6.35 (q, 1H J =7.3 Hz), 1.84 (d, 3H, J = 7.3 Hz). IR (KBr):1674, 1605, 1474, 1383, 1248, 1160, 774, 700 cm^{-1}. EIMS: *m*/*z* 251 (M^++1).

Compound 4p. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.32–7.18 (m, 3H), 7.08–6.95 (m, 5H). IR (KBr):1683, 1600, 1543, 1494, 1441, 1309, 753, 692 cm^{-1}. EIMS: *m*/*z* 268 (M^++1).

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