Tetrahedron 71 (2015) 2168–2176

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solvent-free sonochemical multi-component synthesis of benzopyranopyrimidines catalyzed by polystyrene supported *p*-toluenesulfonic acid

Bodakuntla Thirupathaiah [†], Mudumala Veeranarayana Reddy [†], Yeon Tae Jeong [*]

Department of Image Science and Engineering, Pukyong National University, Busan 608-737, Korea

ARTICLE INFO

Article history:
Received 22 January 2015
Received in revised form 5 February 2015
Accepted 5 February 2015
Available online 19 February 2015

Keywords:
Benzopyranopyrimidines
Ultrasound-mediated condensation
Polystyrene supported *p*-toluenesulfonic
Neat condition

ABSTRACT

An efficient and environment-friendly method for the synthesis of benzopyranopyrimidines has been developed using the ultrasound-mediated condensation of salicylic aldehydes, malononitrile and secondary amines under solvent-free condition at room temperature in the presence of polystyrene supported *p*-toluenesulfonic acid to give the desired product in good to excellent yield. This procedure gives several advantages over current methods including a simple work-up, cost effectiveness, are usable catalyst and shorter reaction times.

1. Introduction

The persistent upsurge in facile and non-polluting synthetic procedures urges synthetic chemists to enlarge tools of their arsenal, because of the increasing distress for the harmful effects of organic solvents on the environment. Ultrasound-promoted synthesis have concerned much consideration during the last few years, and widely utilized to gather speed a number of organic transformations.[1] Simple experimental procedure, clean reaction, short reaction time, high yields, and enhanced selectivity of many ultrasound induced organic transformations offer additional expediency in the field of modern synthetic organic chemistry. Recently, frequent important heterocycles have been synthesized under solvent-free conditions accelerated by ultrasound irradiation.[2]

Multi-component reactions (MCRs) have become increasingly admired tools to guarantee plenty molecular diversity and complexity. They have increased important fame in recent years due to their atom-economy and straight forward reaction design due to substantial minimization of waste, labor, time, and cost. MCRs leading to attractive heterocyclic gibbeted are mainly useful for the building of various chemical libraries of 'drug like' molecules.[3] Several organic reactions have been reported to proceed professionally under solvent-free conditions[4] showing improved selectivity and outstanding yields. Benzopyrano[4,3-d]pyrimidines have engrossed much attention due to their wide range of pharmacological,[5] and biological activities such as *anti*-inflammatory, analgesic importantly, in vitro *anti*-aggregating, antifungal and antibacterial activity.[6]

They also tested for their cytotoxic activity against a panel of cancer cell lines, and a number were shown to cause significant perturbation in cell cycle kinetics.[7] Due to their importance, some methods have been reported for synthesis of benzopyrano[4,3-d] pyrimidines derivatives.[8–16] Although, a number of modified methods under superior conditions have been reported, countless of them suffer from one or more drawbacks, such as unsatisfactory yields, high temperature, long reaction times, and the use of toxic organic solvents and catalysts. Thus, it is necessary to further expand well-organized and appropriate method to build this type of heterocyclic compounds.

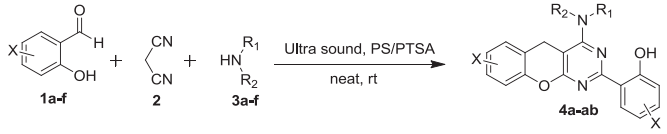
In current years, solid supported catalysts have gained much significance because of cost-effective by reusability and ecological benefits.[17] The environmentally friendly and inexpensively feasible solid acids are increasing incessantly outstanding to their ease of handling and high catalytic activities. Among them, polystyrene-*p*-toluenesulfonic acid (PS/PTSA) complex with a number of compensation such as civilizing the accessibility of active sites, stability, hygroscopic properties, handling, reusability, and good product yields was selected and used as a catalyst in this reaction. This

* Corresponding author. Tel.: +82 51 629 6411; fax: +82 51 629 6408; e-mail address: ytjeong@pknu.ac.kr (Y.T. Jeong).
† These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.tet.2015.02.019
0040-4020/

catalyst in spite of its great reward has not been exploited entirely in organic synthesis.[18]

Our literature investigation at this stage exposed that there are no reports on the synthesis of benzopyranopyrimidines under solvent-free ultrasound irradiation at room temperature (RT) catalyzed by PS/PTSA. Our main approach is to widen a green organic reaction improvement methodology, which is moderately faster and cleaner than conventional reactions. As part of our ongoing research program on the enlargement of clean protocols under solvent-free conditions[4b] herein, we report a facile one-pot synthesis of benzopyranopyrimidines via three-component coupling of salicylic aldehydes, malononitrile and secondary amines under solvent-free ultrasound irradiation at rt (Scheme 1).

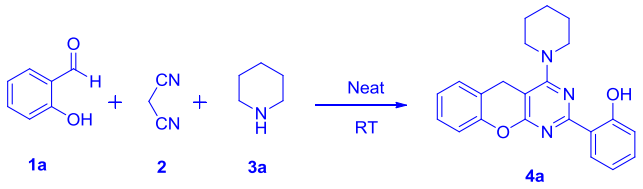


Scheme 1. Sythesis of benzopyrano[4,3-d]pyrimidine derivatives.

2. Result and discussion

To develop optimal reaction conditions, we carried out the reaction between salicyladehyde, (**1a**, 2 mmol), malononitrile (**2**, 1 mmol) and piperdine (**3a**, 1 mmol) as a model rt. It was examined by utilizing different catalysts under both conventional and ultrasound irradiation without solvent. Initially, the model reaction was carried without any catalyst, resulting in poor yields (Table 1, entry 1). This reaction, when conducted using InF_3, CAN-SiO_2, and $ZnCl_2$–SiO_2, produced very low yields (Table 1, entries 2–4). Although catalysts such as $MnCl_2{\cdot}4H_2O$, $Yb(OAc)_3$, $NbCl_5$ and $FePO_4$ promoted the reaction to a considerable extent, the yield of compounds was not satisfactory (Table 1, entries 5–8). But polymer-supported Lewis acid catalysts such as PS/$GaCl_3$, PS/$AlCl_3$, and PS/PTSA (Table 1, entries 9–11) worked efficiently. Among them, PS/PTSA showed excellent catalytic activity under ultrasound irradiation conditions. (Table 1, entry 11). To assert the minimum optimum concentration of the PS/PTSA catalyst, the same reaction was carried out with 10 mg, 20 mg, 30 mg and 40 mg of PS/*P*TSA were used, the yields were 80%, 85%, 94%, and 94%, respectively (Table 1, entries 11–14). It was found that the yield of the products was 81% under conventional conditions and 94% under ultrasound irradiation with 30 mg of the PS/PTSA catalyst in 50 and 15 min, respectively (Table 1, entry 11). Therefore, 30 mg of PS/PTSA was found necessary and sufficient for the total completion of the model reaction in both conditions. The reaction remains incomplete with10 mg, 20 mg of the catalyst (Table 1, entry 12, 13).Therefore, 30 mg of PS/PTSA was sufficient and excessive amount of catalyst did not increase the yields significantly (Table 1, entry 11). Even though using the *P*TSA alone took higher reaction time and smaller yields (Table 1, entry 15).

Table 1
Influence of the catalyst for the synthesis of **4a**[a]

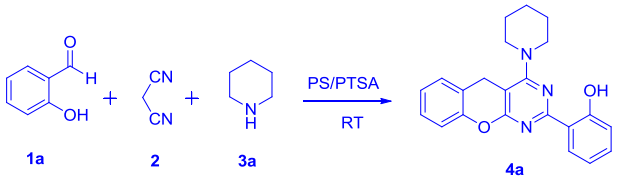


Entry	Catalyst (mol %)	Conventional		Ultrasonic	
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	—	160	20	90	40
2	InF_3 (5)	90	35	50	45
3	CAN-SiO_2 (5)	100	30	60	52
4	$ZnCl_2$–SiO_2 (5)	120	40	70	48
5	$MnCl_2{\cdot}4H_2O$ (5)	100	50	60	70
6	$Yb(OAc)_3$ (5)	110	45	80	55
7	$NbCl_5$ (5)	80	55	45	65
8	$FePO_4$ (5)	95	45	60	70
9	PS/$GaCl_3$ (30 mg)	65	70	30	80
10	PS/$AlCl_3$(30 mg)	60	72	30	85
11[c]	PS/PTSA (30 mg)	50	81	15	94, 91, 90, 87
12	PS/PTSA (10 mg)	70	60	30	80
13	PS/PTSA (20 mg)	60	75	25	85
14	PS/PTSA (40 mg)	50	81	15	94
15	*P*-TSOH (5)	65	75	30	85

[a] Reaction of salicylaldehyde (2 mmol), malononitrile (1 mmol), piperdine (1 mmol) under solvent-free condition at rt.
[b] Isolated yields.
[c] Catalyst was reused three times.

The effect of solvent on the model reaction was studied in both conventional and ultrasound irradiation using 30 mg of PS/PTSA in different solvents and without solvent at rt. Irrespective of the nature of the solvent, the yield of the products was low (Table 2, entries 1–5). But under solvent-free conditions, better yield of product resulted (Table 2, entry 6). The poor yields in the solvent medium may be attributed to solvation of the substrates in the reaction medium. Therefore, it is established that ultrasound irradiation at rt without the solvent is the best condition for this reaction.

Table 2
Screening of various solvent for the synthesis of compound **4a**[a]



Entry	Solvent (5 mL)	Conventional		Ultrasonic	
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	Acetonitrile	75	55	45	70
2	Dichloromethane	90	35	40	65
3	Tetrahydrofuran	50	75	35	80
4	Methanol	60	70	30	78
5	Ethanol	60	75	60	70
6	Neat	50	81	15	94

[a] Reaction of salicylaldehyde (2 mmol), malononitrile (1 mmol), piperdine (1 mmol), PS/PTSA catalyst (30 mg) at rt.
[b] Isolated yields.

The recyclability of the PS/PTSA catalyst was also established by running the same model reaction in three cycles with recovered PS/PTSA and obtained **4a** in 94, 91, 90 and 87% product yield. This proved that efficiency of the catalyst can be used for multiple usage purpose without much loss of its efficiency (Table 1, entry 11). From these all establishments (Table 1) concluded that 30 mg of PS/PTSA, solvent-free at rt under ultrasound irradiation are optimized reaction conditions for the synthesis of benzopyranopyrimidines.

Under these optimized set of experimental reaction conditions, the condensation of malononitrile (**2**) with different salicylic aldehydes (**1a**–**f**) and various secondary amines (**3a**–**f**) was carried out and obtained a variety of benzopyranopyrimidines (**4a**–**4ab**) and the results were described in Table 3. As shown in Table 3, in all cases, with either electron-donating or electron-withdrawing groups on salicylaldehydes reacted smoothly with malononitrile and secondary amines in the presence of 30 mg PS/PTSA at rt to form the corresponding benzopyrano[2,3-d]pyrimidines in good to excellent yields without formation of any side products. This catalyst worked excellently with either electron-donating or electron-withdrawing groups on salicylaldehydes.