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Original Research Article

Efficient protocol for the production of pyrimido[4,5-*b*] quinolines using an organic-inorganic hybrid catalyst

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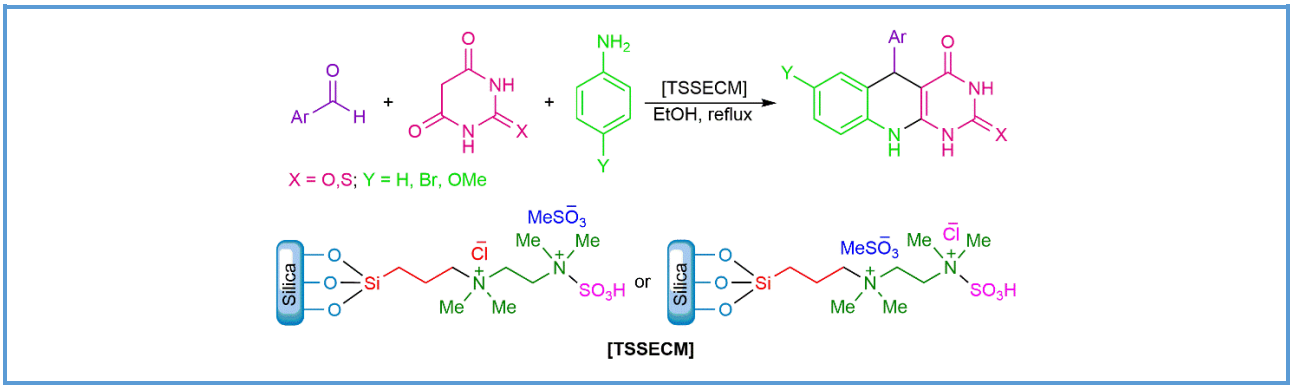
N,N,N′,N′-Tetramethyl-*N*-(silica-*n*-propyl)-*N′*-sulfonic acid-ethylenediaminium chloride/mesylate ([TSSECM])

Multi-component reaction

ABSTRACT

In this work, an efficient protocol for the synthesis of pyrimido[4,5-*b*]quinolines was reported. The one-pot multi-component reaction of arylaldehydes, barbituric acid (or 2-thiobarbituric acid) and anilines in the presence of an organic-inorganic hybrid material namely tetramethyl-*N*-(silica-*n*-propyl)-*N′*-sulfonic acid-ethylenediaminium chloride/mesylate ([TSSECM]) afforded the mentioned compounds. This protocol has several advantages including, high yields (86-95%), relatively short reaction times (110-120 min), recyclability of the catalyst and easy purification of the products without column chromatography.

Graphical Abstract



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Introduction

Multi-component reaction (MCR) is utilized as a useful technique in organic synthesis wherein complex molecules can be easily produced. In MCRs, three or more starting materials are reacted in a one-pot system, and produce a single or main product. This kind of reactions is associated with easy operation, effectiveness, saving time and energy, high atom economy and green nature [1–6].

Organic-inorganic hybrid materials have some unique characteristics, such as suitable durability (thermal and chemical), green nature, designable for applications in different medicinal and industrial fields, non-corrosiveness and easy separation from the process reactor [7–18]. For example, they have been applied to remove lead from wastewater [7], and as drug carrier [8], semiconductor [9], and catalysts for organic reactions [10–18].

The compounds having pyrimido-quinoline moiety are of importance in pharmacological field. Pyrimido[4,5-*b*]quinolines, as a class of these compounds, have a wide range of medicinal activities, e.g. anti-allergy [19], antimicrobial [20], anti-inflammatory [21], anticancer [22], antioxidant [23], analgesic [23], antifungal [24], and antibacterial [24] properties. A simple protocol for the syntheis of pyrimido[4,5-*b*]quinolines include the one-pot multi-component reaction of arylaldehyde, barbituric acid (or 2-thiobarbituric acid) and anilines; some catalysts have been reported in the literature to promote this reaction, e.g. *L*-proline [25], oxalic acid dehydrate-proline mixture [26], β-cyclodextrin [27], 1,4-diazabicyclo[2.2.2]octane [28], and SPION@glutathione [29]. Moreover, UV365 light has been used for the catalyst-free production of pyrimido[4,5-*b*]quinolines in aqueous-glycerol medium [30]. In is noteworthy that a few catalysts have been reported for the synthesis of pyrimido[4,5-*b*]quinolines from arylaldehyde, barbituric acid (or 2-thiobarbituric acid) and anilines; thus, it is desirable to introduce new catalysts for this reaction.

In this work, we have prepared pyrimido[4,5-*b*]quinolines *via* the one-pot multi-component reaction of arylaldehyde, barbituric acid (or 2-thiobarbituric acid) and anilines using tetramethyl-*N*-(silica-*n*-propyl)-*N*′-sulfonic acid-ethylenediaminium chloride/mesylate ([TSSECM]) as an efficient organic-inorganic hybrid catalyst.

Experimental

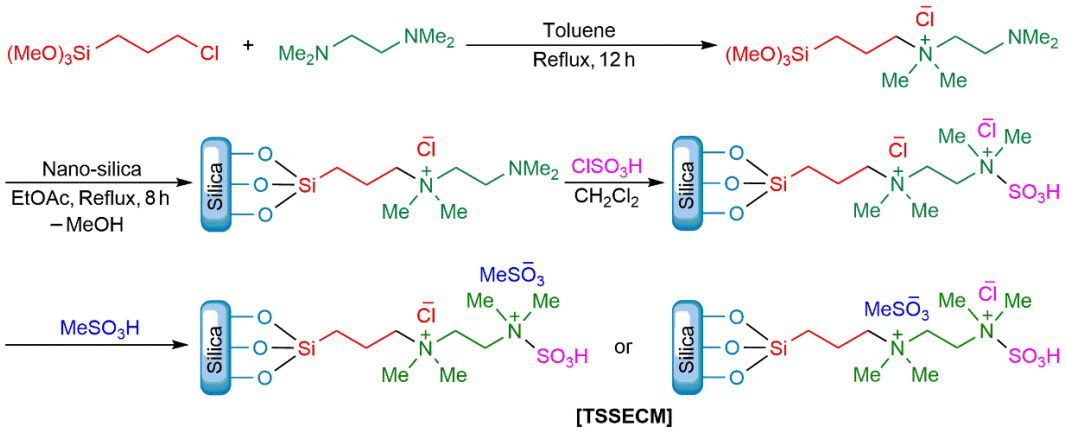
Materials and methods

All the chemicals were purchased from the Fluka or Merk Chemical Companies. [TSSECM] was prepared according to our reported procedure (Scheme 1) [10]; most particles of [TSSECM] were in nano-size, and some particles were larger than 100 nm. The reaction progress was observed by thin layer chromatography (TLC). The melting points were registering on a Thermo Scientific 9200 apparatus in open capillary tubes. FT-IR was run on a Bruker apparatus (model: Tensor 27, Germany). The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were run on a Bruker Avance DPX FT-NMR spectrometer. Mass spectra were recorded on a spectrometer 5975C VL MSD model triple-axis detector.

General procedure for the production of pyrimido[4,5-b]quinolines

A mixture of aldehyde (1 mmol), barbituric acid (0.128 g, 1 mmol) [or 2-thiobarbituric acid (0.144 g, 1 mmol)], aniline (1 mmol) and [TSSECM] (0.016 g) was stirred in EtOH (3 mL) under reflux conditions. After consuming the reactants (as confirmed by TLC), the EtOH was evaporated, EtOAc (10 mL) was added, stirred

for 1 min in reflux conditions, centrifuged and decanted to isolate the insoluble catalyst (this action was repeated three times). After combining the solutions resulted from the decanting, the solvent (EtOAc) was evaporated, and the residue was recrystallized from EtOH (95%) to offer the pure product.



Scheme 1. The preparation of [TSSECM]

Selected spectral data of products

Compound 1b

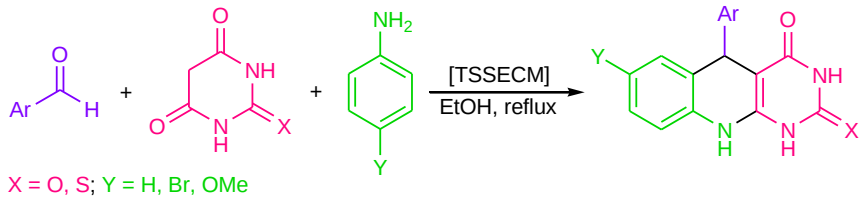
^{1}H NMR (500 MHz, DMSO-d$_6$): δ 6.04 (s, 1H, methine hydrogen), 6.95-6.97 (m, 2H, H$_{Ar}$), 7.34 (d, J = 8.6 Hz, 1H, H$_{Ar}$), 7.38 (br, 1H, NH), 7.45 (d, J = 8.3 Hz, 2H, H$_{Ar}$), 8.10 (d, J = 8.5 Hz, 2H, H$_{Ar}$), 10.35 (br., 2H, NH). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ (ppm) 32.4, 115.3, 121.9, 123.3, 123.5, 124.1, 124.6, 128.6, 130.4, 132.7, 145.7, 150.8, 151.1, 154.1, 165.4.

Compound 1f

IR (KBr) (ν_{max}/cm^{-1}): 3406, 3192, 3089, 2974, 1625, 1609, 1535, 1511, 1445, 1350, 1259, 1204. ^{1}H NMR (500 MHz, DMSO- d$_6$): δ 3.77 (s, 3H, CH$_3$O), 6.09 (s, 1H, methine hydrogen), 7.03-7.05 (m, 2H, H$_{Ar}$), 7.26-7.28 (m, 2H, H$_{Ar}$), 7.48-7.52 (m, 2H, H$_{Ar}$), 7.79 (s, 1H, NH), 7.98 (d, J = 7.4 Hz, 1H, H$_{Ar}$), 9.64 (s, 2H, NH). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ (ppm) 31.3, 56.1, 95.7, 115.1, 115.5, 120.9, 121.5, 124.6, 125.0, 129.9, 134.3, 146.6, 148.3, 159.4, 163.4, 173.7. Mass: m/z 382 (M$^+$).

Results and Discussion

To find appropriate conditions for the production of pyrimido[4,5-*b*]quinolines, the reaction of 4-nitrobenzaldehyde (1 mmol), barbituric acid (1 mmol) and 4-bromoaniline (1 mmol) (Scheme 2) was studied in the presence of different amounts of [TSSECM] in some solvents and solvent-free conditions; the results are briefed in Table 1. The reaction yield was not good in the absence of solvent (entry 1). The best results were obtained when the reaction was performed using 0.016 g of the catalyst in EtOH under reflux conditions (entry 5, optimal conditions). The other solvents (MeCN, THF and EtOAc) afforded the product in lower yields and longer reaction time compared with EtOH (entries 2-4). Performing the reaction at 70 ºC in EtOH decreased the yield (entry 6). Furthermore, increment the catalyst amount up to 0.018 g didn't improve the results (entry 7).



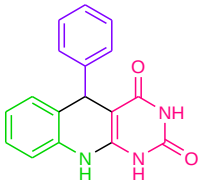
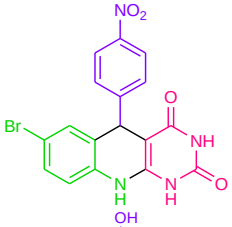
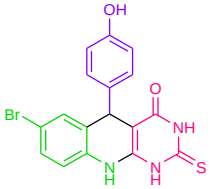
Scheme 2. The model reaction

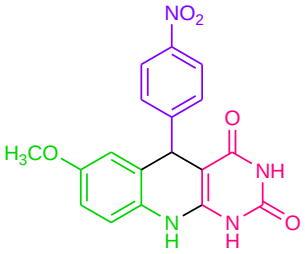
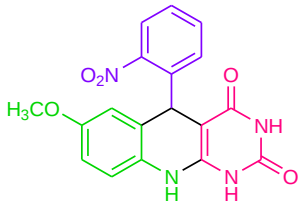
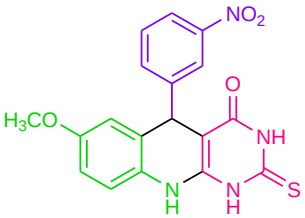
Table 1. Studying influence of temperature, the catalyst amount and solvent on the model reaction

Entry	Solvent	The catalyst amount (g)	Temp. (°C)	Time (min)	Yield (%)
1	Solvent-free	0.016	80	30	72
2	MeCN	0.016	Reflux	180	93
3	THF	0.016	Reflux	180	77
4	EtOAc	0.016	Reflux	180	84
5	EtOH	0.016	Reflux	120	95
6	EtOH	0.016	70	120	87
7	EtOH	0.018	Reflux	120	95

To assess the efficacy and scope of our method, some arylaldehydes were reacted with barbituric acid (or 2-thiobarbituric acid) and anilines under the optimal conditions; the results and the produced pyrimido[4,5-*b*]quinolines are illustrated in Table 2. As can be seen in Table 2, the reaction times were relatively short in all cases (110-120 min). Moreover, all substrates including benzaldehyde, arylaldehydes bearing electron-withdrawing and electron-releasing substituents on *ortho*, *meta* and *para* positions, barbituric acid, 2-thiobarbituric acid, aniline, 4-bromoaniline and 4-methoxyaniline afforded pyrimido[4,5-*b*]quinolines in high yields. These results confirmed high efficacy and generality of our method.

Table 2. The preparation of pyrimido[4,5-*b*]quinolines using [TSSECM]

No.	Product	Time (min)	Yield[a] (%)	M.p. °C (Lit.)
1a		120	93	222-224 (224-226) [30]
1b		120	95	242-244 (238-240) [30]
1c		120	86	331-333 (335-339) [25]

1d		110	96	230-232 (231-233) [30]
1e		120	90	187-190 (183-190) [25]
1f		120	91	237-240 (This work)

[a]Isolated yield

To study the ability of [TSSECM] to recycle and reuse, the synthesis of compound **1d** was selected. The catalyst was recycled according to the procedure mentioned in the experimental section, and reused; the results are indicated in Figure 1. [TSSECM] was recyclable for one time with partial decrement of its catalytic activity. In second recycling (run 3), the reaction time increased up to 160 min, and the yield decreased to 83%.

Considering the literature [25–27] and dual-functionality of the catalyst [10], a plausible mechanism was proposed for the reaction (Scheme 3). The roles of SO_3H (acidic group) in [TSSECM] include: (i) activating the electrophiles to accept nucleophiles (and performing steps 1, 3 and 4), (ii) helping for removal of H_2O (steps 2 and 5), and (iii) acceleration of tautomerization (step 6). The tasks of mesylate anion (as a weak basic group) in the catalyst consist of: (i) activation of nucleophiles to carry out steps 1, 3 and 4, (ii) assistance to remove H_2O in step 5, and (iii) acceleration of tautomerization (step 6).

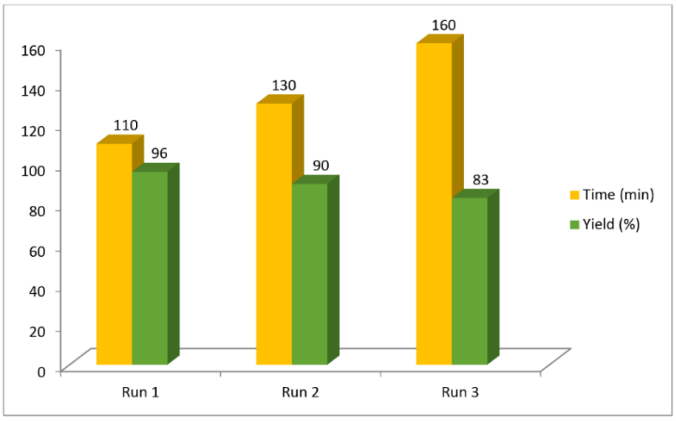
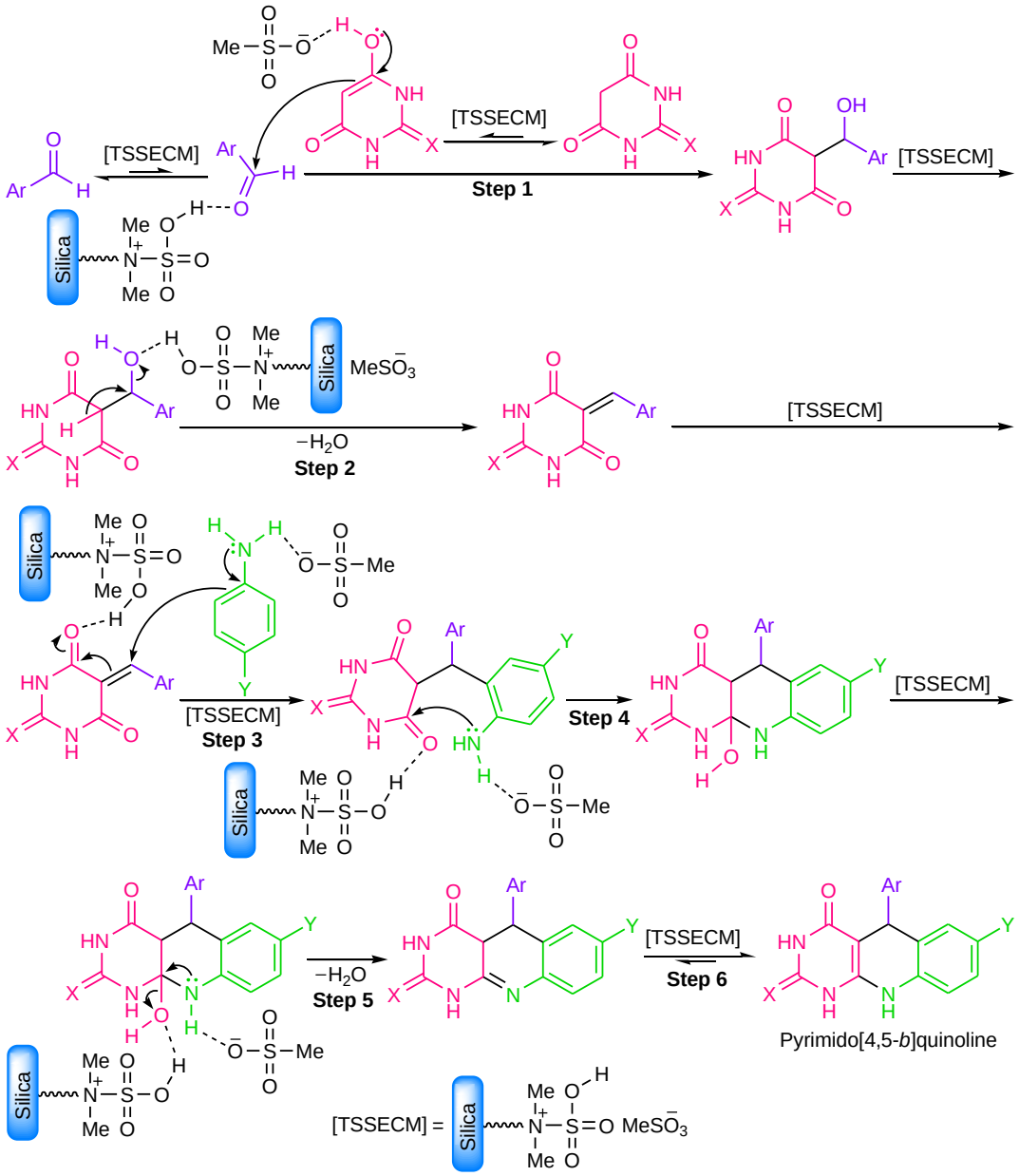


Figure 1. The results on reusability of [TSSECM] for the production of compound **1d**



Scheme 3. The proposed mechanism

Conclusions

In this research study, we introduced [TSSECM] as new catalyst for the production of pyrimido[4,5-*b*]quinolines. The advantages of this work can be pointed to application of small amount of catalyst in reaction, relatively short reaction times (110-120 min), high yields (86-95%), effectiveness, no need to column chromatography for purification of the products and recyclability of the catalyst.

Acknowledgements

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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