Research Article

SULFATED TIN OXIDE (STO)-CATALYZED EFFICIENT SYNTHESIS OF 1,8-DIOXO-DECAHYDROACRIDINES

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Abstract

This study introduced a solvent-free synthesis of 1,8-dioxodecahydroacridine derivatives through a one-pot condensation reaction involving cyclic 1,3-diketone and aldehydes, utilizing sulfated tin oxide (STO) as a heterogeneous catalyst, achieving yields of up to 93%. The current methodology presents numerous advantages, including low cost, a recoverable and reusable catalyst (up to three times), a solvent-free strategy, straightforward setup, high yield, and reduced reaction time, effectively highlighting the environmentally friendly nature of the present reaction.

Keywords:

Sulfated tin oxide (STO); 1,8-dioxodecahydroacridines; catalysis; recyclability; multicomponent reactions (MCRs).

Introduction

Concurrent research in organic synthesis emphasizes economic efficiency. Assessment of the efficiency of a chemical synthesis involves evaluating several parameters, such as selectivity and overall yield. Additionally, factors concerning raw materials, time, human resources, and energy requirements must also be considered. Additionally, the toxicity and hazards associated with the chemicals and protocols involved are also important factors to evaluate. It is now acknowledged that the step count serves as a critical criterion in assessing the efficiency of a synthesis.

In this context, multicomponent reactions (MCRs) have emerged as effective and efficient tools for bond formation in organic, combinatorial, and medicinal chemistry.[1-2] The MCRs strategy provides considerable benefits compared to traditional multistep synthesis, owing to its flexible, convergent, and atom-efficient characteristics. MCRs exemplify environmentally sustainable practices by minimizing the number of steps involved, lowering energy consumption, and decreasing waste generation.[3-4]

Solid heterogeneous catalysts provide notable benefits in synthetic chemistry, such as easy regeneration, reduced corrosiveness, lower costs, ease of handling, and efficient reuse.[5-8] Sulfated tin oxide, referred to as SO_4^{-2}/SnO_2 (STO), has emerged as a widely recognized and effective catalyst owing to its extensive surface area, high efficiency, non-corrosive properties, cost-effectiveness, and broad surface area. Commonly employed in chemical and industrial environments,[9-29] it consists of sulfated and sulfonic acid groups on various heterogeneous solid substrates.

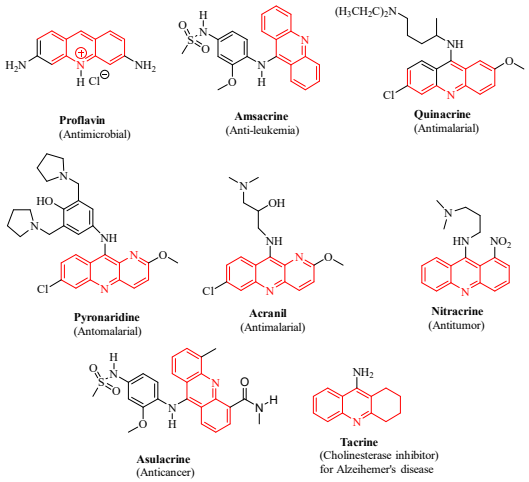


Fig. 1. Some acridine derivatives in clinical use

Acridines that contain the polyfunctionalized 1,4-dihydropyridine (DHPs) parent nucleus exhibit notable pharmaceutical properties, including positive ionotropic effects that facilitate the entry of calcium into the intracellular space. Additionally, 1,8-acridinediones are recognized for their application as laser dyes. These derivatives serve as luminous agents in spectroscopy and function as semiconductors in material science. The DHP derivatives are recognized for their extensive biological and pharmacological activities, including antitumor, antitubercular, antimalarial, antibacterial, antihypertensive, fungicidal, anticancer, and anti-inflammatory properties, as well as their potential in treating Alzheimer's disease and angina pectoris. Examples of published derivatives of acridines along with their biological activities are presented in the following **Fig. 1**.[30-32]

1,8-Acridinediones were synthesized using the Hantzsch procedure, which involves the thermal reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with an aldehyde and ammonia. Many methods involving various catalysts have been previously reported. These methods typically require extended reaction times, yield 1,4-dihydropyridines at relatively low levels, and often involve the use of harmful organic solvents.[33-34] The synthesis of 1,8-dioxodecahydroacridine presents opportunities for further innovation in methodologies that utilize milder reaction conditions, reduce reaction times, allow for greater variation in substituents, and enhance yields. It is essential to explore innovative methodologies that utilize new and efficient catalysts. This represents an ongoing commitment to advancing innovative methodologies for diverse organic transformations.[14,35] This report presents an effective method for synthesizing 1,8-dioxodecahydroacridine derivatives *via* a one-pot, three-component cyclization reaction, catalyzed by STO in acetonitrile as the solvent.

Experimental

Typical procedure for the synthesis of acridinediones:

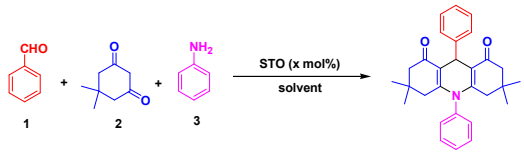
A mixture of dimedone (2 mmol), an appropriate aromatic aldehyde (1 mmol), ammonium acetate (1.2 mmol) or amine derivative (1 mmol) and 10 mol% of STO catalyst in acetonitrile (2 mL) was refluxed for the time specified in **Table 1**. The reaction was monitored by TLC using petroleum: ethyl acetate (4:1) as eluent. After completion of the reaction, boiling ethanol was added to the mixture and the catalyst was removed by filtration and the filtrate was concentrated under vacuum. The product was purified by recrystallization from ethanol.The desired products of purity were further achieved by column chromatography with petroleum ether/ethyl acetate to provide the analytically pure product. Compounds were characterized by using IR, ^{1}H NMR, and ^{13}C NMR.

Representative spectral data of compound 4d (3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-10-phenyl-3,4,6,7,9,10-hexahydro-1,8-(2*H*,5*H*)-acridinedione): **m.p.**243-245 ^{0}C; **^{1}H-NMR ($CDCl_3$):** δ 0.73 (s, 6H, CH_3), 0.85 (s, 6H, CH_3), 1.76 (d, J = 17.6 Hz, 2H, CH_2), 2.02 (d, J = 17.5 Hz, 2H, CH_2), 2.04 (d, J = 16.2 Hz, 2H, CH_2), 2.13

(d, J = 16.2 Hz, 2H, CH_2), 5.19 (s, 1H, CH), 7.13 (d, J = 8.29 Hz, 2H, ArH), 7.17 (d, J = 7.81 Hz, 2H, ArH), 7.31 (d, J = 8.29 Hz, 2H, ArH), 7.49 (m, 3H, ArH).

Results and Discussion

This study involves the substitution of ammonium acetate with aniline for the synthesis of decahydroacridine-1,8-diones via the Hantzsch reaction, utilizing a STO catalyst under different reaction conditions (**Scheme 1**). We commenced our investigation by conducting a reaction involving benzaldehyde (**1**), 1,3-cyclohexadione (**2**) and aniline (**3**) utilizing STO (20 mol%) across various solvents as well as under solvent-free conditions. Acetonitrile has been identified as the optimal solvent among those tested (entry 3). Under controlled conditions, the reaction is observed to be ineffective (entry 6). The catalytic efficiency of STO was clearly demonstrated by the incomplete conversion observed even after 24 hours without the catalyst present. Following the selection of the solvent, the model reaction was evaluated utilizing various catalyst loadings of STO. We observed that 10 mol% of catalyst is effective for the desired transformation (**4a**), demonstrating favorable results in both yield and reaction time. The optimized reaction parameters are as follows: STO (10 mol%) in acetonitrile under reflux conditions, conducted in open air.



Scheme 1. Screening of reaction conditions[a]

entry	solvent/reflux (20 mol% STO)	time (h)	yield (%)[a]
1	CH_2Cl_2	2	NR
2	toluene	1.5	58
3	**CH_3CN**	**1**	**90**
4	$CHCl_3$	1	48
5	EtOH	1.5	26
6	Neat/80 °C	-	NR

entry	catalyst (mol%)/CH_3CN	time (h)	yield (%)[a]
1	5	2	17
2	7.5	1.5	63
3	**10**	**1**	**89**
4	20	1	90
5	-	24	nr

[a] Isolated yield

Scheme 1. STO-catalyzed synthesis of decahydroacridine-1,8-diones

In order to assess the scope and limitations of the methodology, reactions were conducted using a range of substituted benzaldehydes, which included both electron-donating and electron-withdrawing groups on the aromatic ring (entries 4a-h, **Table 1**). The findings indicated that the yields of *N*-substituted acridinediones for aromatic aldehydes containing an electron-withdrawing group surpass those for aromatic aldehydes with electron-donating groups. Substitutions on the aniline counterpart were also explored, and the reaction scope yielded positive results (entries **4i-4l**, **Table 1**). All were acquired in a relatively short duration (1-4.5 hours). The catalyst, which is both recoverable and reusable, demonstrated no significant loss of the desired product over three cycles (4a, 85%). The catalyst is capable of being filtered, oven dried at 100 °C, and reused for a minimum of three cycles without a substantial loss of the desired product.

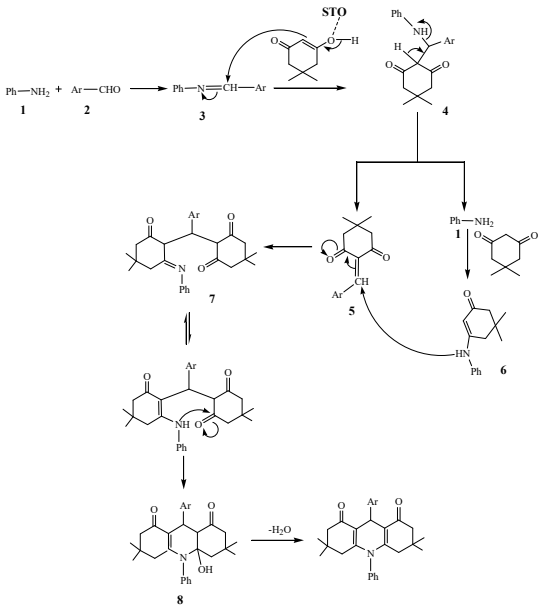
Table 1. STO-Catalyzed multicomponent synthesis of 1,8-dioxodecahydroacridines[a]

Entry	Aldehyde	Aniline	Product	Time (h)	Yield (%)
1	C_6H_5CHO	$PhNH_2$	**4a**	1	89
2	4-Me-C_6H_4CHO	$PhNH_2$	**4b**	3.0	85
3	4-OMe-C_6H_4CHO	$PhNH_2$	**4c**	3.0	82
4	4-Cl-C_6H_3CHO	$PhNH_2$	**4d**	2.5	90
5	4-NO_2-C_6H_4CHO	$PhNH_2$	**4e**	1.5	93
6	4-CN-C_6H_4CHO	$PhNH_2$	**4f**	1.0	78
7	3-NO_2-C_6H_4CHO	$PhNH_2$	**4g**	1.0	88
8	4-OH-C_6H_4CHO	$PhNH_2$	**4h**	2.5	80
9	C_6H_5CHO	4-Me-$C_6H_4NH_2$	**4i**	2.0	82
10	4-Cl-C_6H_4CHO	4-Me-$C_6H_4NH_2$	**4j**	2.0	85
11	4-NO_2-C_6H_4CHO	4-Cl-$C_6H_4NH_2$	**4k**	1.5	83
12	4-OH-C_6H_4CHO	4-NO_2-$C_6H_4NH_2$	**4l**	4.5	82

[a]Isolated yields

The formation of 1,8-dioxodecahydroacridines can be explained by the initial creation of the imine, which is catalyzed by STO, resulting from the condensation of aromatic aldehydes **2** with the corresponding aniline **1** (**Scheme 2**). The attack of the enol form of dimedone on the imine **3** leads to the formation of adduct **4**, which subsequently undergoes an internal rearrangement to yield aniline 1 and arylidenes **5**. The released aniline 1 may react with another molecule of dimedone to yield the amino enone **6**, which could subsequently engage its nucleophilic amino group with the electrophilic carbon atom of the former arylidene, resulting in the formation of the new imine **7**. The unstable imine may rearrange into the relatively stable structure of the hydroxy hydroacredindiones **8**, which can ultimately stabilize into the title structure of 1,8-

dioxodecahydroacridines through the elimination of a molecule of water.



Scheme 2. STO-Catalyzed synthesis of 1,8-dioxodecahydroacridines-Proposed mechanism

Conclusion

In conclusion, we developed a solvent-free approach for the synthesis of 1,8-dioxo-decahydroacridines from aromatic aldehydes, an amine, and a dimedone employing STO catalyst as an effective solid acid catalyst. The primary advantages of this technology are its reasonable reaction times, excellent yields, straightforward workup process, recyclable, reusable, and heterogeneous conditions.

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Conflict of interest

All authors declare that they have no conflict of interest.

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NA

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