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Metal-free efficient thiolation of C(sp^2) functionalization *via in situ*-generated NHTS for the synthesis of novel sulfenylated 2-aminothiazole and imidazothiazole†

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A direct metal-free approach for the synthesis of novel sulfenylated 2-aminothiazole and imidazothiazole derivatives at room temperature is reported *via* an *in situ*-generated electrophilic thiolating agent. The present protocol provides mild and selective access for the insertion of C–S bond functionalization with good yield. The mechanistic path was justified *via* density functional theory (DFT) calculations, which explore the role of the solvent in the reaction mechanism.

Introduction

The prevalent occurrence of organosulfur compounds in vital biological systems, drug architectures and natural products present themselves as versatile scaffolds in organic chemistry, medicinal chemistry and materials chemistry.[1–5] They constitute an active portion of commercially available drugs.[6,7] These consequences have led to an unending quest for a capable catalytic system, comprising a blend of carbon-sulfur bonds to create organosulfur compounds.[8–16] The majority of reported transformations for C–S bond coupling includes the synthesis of diaryl sulfides using imidazoheterocycles,[17–20] indoles[21–25] or aryl halides[26–30] by reaction with thiols or thiones. Several catalytic systems utilized for the cross dehydrogenative coupling reaction (CDC) of the C–S bond include the use of transition metals,[31–36] elemental sulfur,[37–39] and iodine.[40–44] Amongst these protocols, those capable of encountering direct metal-free regioselective C–S bond coupling in bifunctional motifs for the selective synthesis of heterocyclic organosulfur compounds are highly desirable.[45–52] Moreover, among numerous catalytic systems reported for the synthesis of organosulfur compounds, the use of *N*-halosuccinimides was proven to be a highly useful approach;[53–59] however, *N*-halosuccinimides have a general tendency to oxidise secondary alcohols to their corresponding ketones.[60,61] In recent years, the use of *N*-sulfanylsuccinimides for the direct sulfenylation of aromatic and heteroaromatic C–H bonds has become an interesting strategy.[62–73] Very few reports are available for the synthesis of catechol thioethers.[75–77] However, the selective synthesis of organosulfur compounds has not been reported hitherto *via in situ*-genarated *N*-(heteroarylthio)-succinimide (NHTS), by utilizing *N*-halosuccinimide and heterocyclic thiols such as 1H-benzo[*d*]imidazole-2-thiol, benzo[*d*]oxazole-2-thiol and 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol. The use of these heterocyclic thiols may impart advantages in the areas of small molecule syntheses as well as pharmaceuticals as imidazothiazole and thiazoles are considered to possess a broad spectrum of biological activity.[79,80] Consequently, the selective C-5 electrophilic sulfenylation of pseudo aromatic imidazothiazoles with secondary alcohols may provide a beneficial synthetic route for medicinal chemistry research. Jie *et al.* have reported the organocatalytic sulfenylation of β-naphthols using *N*-(arylthio)succinimide as the sulfur source, and they have observed that the dearomatization of β-naphthols takes place with the oxidation of an alcoholic group to a ketone (Scheme 1).[78]

Nevertheless, alcohols also possess the propensity to react with thiols to generate thioethers in the presence of certain catalytic systems.[81–86] These annotations and our previous study regarding the synthesis of bioactive compounds[87–89] have provoked us to focus on the development of a new catalytic system for the selective C(sp^2)–H bond thiolation of 2-aminothiazoles and imidazothiazoles using heterocyclic thiols and *N*-halosuccinimide.

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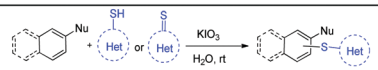
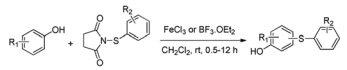
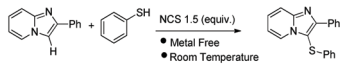
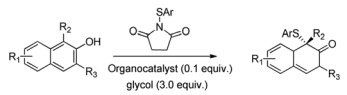
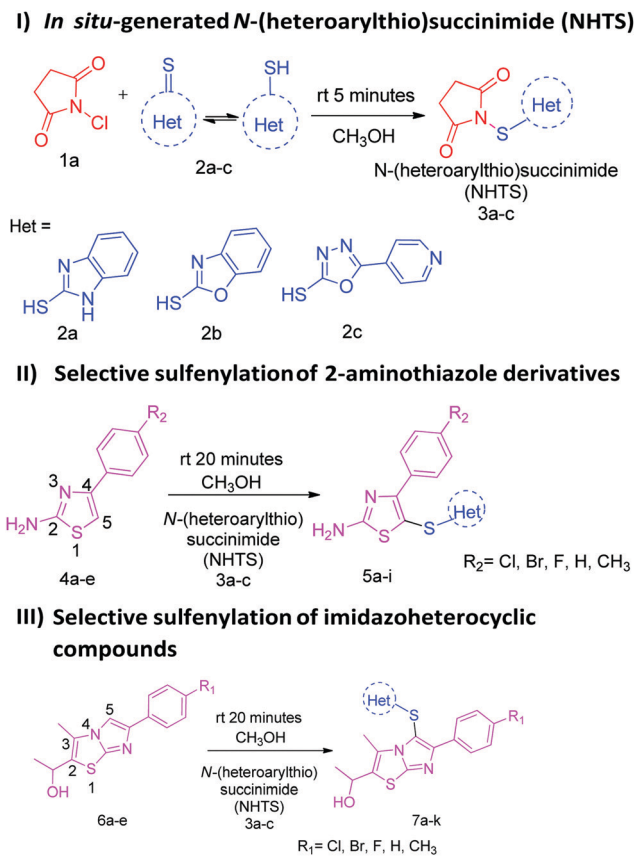
Sr. No.	Scheme	Time	Ref. No.
a)		15 h	72
b)		0.5 h	73
c)		30 min	74
d)		30 min	53
e)		75 h	78

Scheme 1 Earlier approaches for C–S bond coupling.

Results and discussion

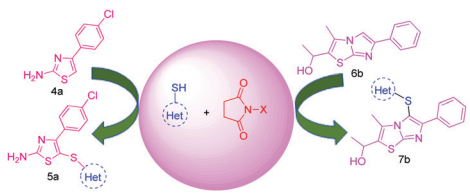
The hypothesized synthetic route commences with the reaction of *N*-chlorosuccinimide with aromatic thiophenols, as predicted by previous literature.[53] We have further demonstrated that further reaction of *N*-chloro-thiols smoothly allows the formation of C–S bonds.[53,74] When this halogenation-thiolation tandem strategy was first implemented, the formation of the product took place with poor yield and prolonged time of 10 h.

When we carried out the same reaction taking 1 equiv. of *N*-chlorosuccinimide with 1 equiv. of 1H-benzo[*d*]imidazole-2(3H)-thione using methanol as the solvent, we came across a curious observation that instead of introducing chlorination in heterocyclic thione, the construction of *in situ*-generated NHTS (Scheme 2I) takes place within 5 min by stirring at room temperature. A plausible reason for this observation may be that the resonance stability of heterocyclic thiols eventually supports the *in situ* generation of NHTS. When the same strategy was employed in the case of aromatic thiols, the generation of *N*-(arylthio)succinimide does not take place to such an extent. We investigated the utilization of NHTS for the sulfenyllation of substituted 4-phenylthiazol-2-amine **4a–e** (Scheme 2II) and 1-(3-methyl-6-phenylimidazo[2,1-*b*]thiazol-2-yl)ethanol **6a–e** (Scheme 2III) in the same reaction pot. The starting reactant **6a–e** was obtained by reducing 1-(5-((1H-benzo[*d*]imidazol-2-yl)thio)-6-(4-chlorophenyl)-3-methylimidazo[2,1-*b*]thiazol-2-yl)ethenone with $NaBH_4$.[90] For exploring the optimal reaction conditions, *N*-halosuccinimide and solvents were examined using 4-(4-chlorophenyl)thiazol-2-amine or 1-(3-methyl-6-phenylimidazo[2,1-*b*]thiazol-2-yl)ethanol as the standard reactant (Table 1). Initially, *N*-chlorosuccinimide (NCS) 1 equiv. was employed under dichloromethane (DCM) as the solvent yield was observed to decrease (Table 1, entry 1). When the amount of NCS was increased, the yield improved (Table 1, entry 2). Further improvement of the yield was seen when 1.5 equiv. of NCS was employed with 2 equiv. of the reactant (Table 1, entry 3). Optimized reaction conditions were found when methanol was used as the solvent with 1.5 equiv. of NCS and 2 equiv. of reactant



Scheme 2 Present work.

Table 1 Optimal reaction condition[a]



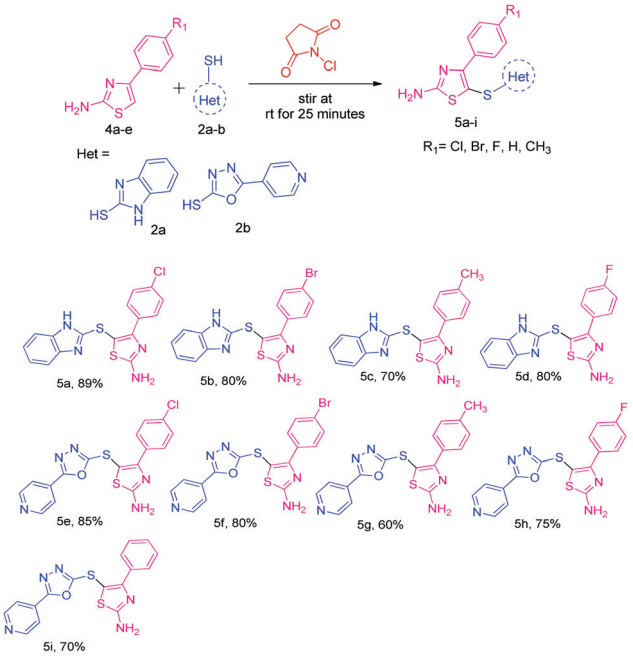
Entry	NXS equiv.	Heterocyclic thiols equiv.	Solvent (3 ml)	Yield[b] (%)
1	NCS (1.0)	1	DCM	43
2	NCS (1.5)	1	DCM	47
3	NCS (1.5)	2	DCM	52
4	NCS (1.5)	1	CH_3OH	71
5	NCS (2.0)	1	CH_3OH	64
6	**NCS (1.5)**	**2**	**CH_3OH**	**89**
7	NCS (1.5)	2	CH_3COOH	34
8	NCS (1.5)	2	Toluene	41
9	NCS (1.5)	2	CH_3CN	44
10	NCS (1.5)	2	DMF	31
11	NCS (1.5)	2	DMSO	51
12	NIS (1.5)	2	CH_3OH	58
13	NBS (1.5)	2	CH_3OH	78
14	—	2	CH_3OH	NR[c]
15	NCS (1.5)	2	No solvent	Trace

[a] Reaction conditions: *N*-halosuccinimide, heterocyclic thiols are stirred for 5 min at room temperature first and then reactant **4a** or **6a** was added and reaction mass was further stirred for next 20 min at room temperature. [b] Isolated yield. [c] NR = No reaction.

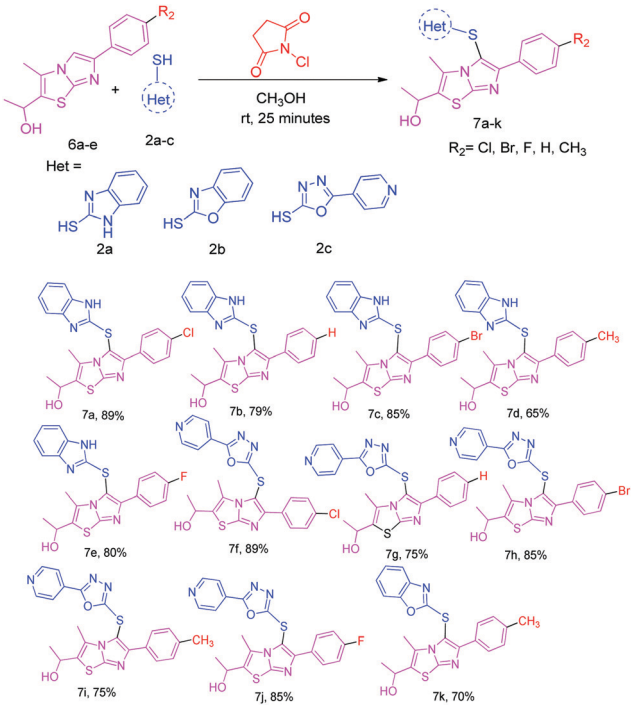
(Table 1, entry 6). The as-synthesized product was washed with cold ethanol. Column chromatography was not needed for purification. Further variation in the amount of the reactant and/or NCS using methanol as the solvent was shown to decrease the yield (Table 1, entries 7–11). The implementation of *N*-iodosuccinimide or *N*-bromosuccinimide was observed to diminish the yield (Table 1, entries 12 and 13). In absence of *N*-halosuccinimide the reaction did not proceed (Table 1, entry 14). Furthermore, the reaction was not observed under solvent-free conditions (Table 1, entry 15).

With this optimal set of reaction conditions (Table 1, entry 6), we proceeded to investigate the sulfenylation of 2-aminothiazole derivatives. While exploring the effects of the substrate scope of 2-aminothiazole derivatives, the unsubstituted 2-aminothiazole ring at the C-4 position was unable to furnish the product. Amongst the substituted 2-aminothiazole derivatives, those derivatives possessing electron withdrawing substituents at the para position of the aromatic ring successfully furnished the product with satisfactory yield (Scheme 3). Electron-donating groups were found to retard the yield (Scheme 3), while substituents at the meta position were unable to furnish the product.

Interestingly, the method achieves the selective C-5 sulfenylation of 2-aminothiazole derivatives, and no reactions were observed to give a nuclear sulfenylation product. We further proceeded to investigate numerous 1-(3-methyl-6-phenylimidazo[2,1-*b*]thiazol-2-yl)ethanol derivatives for their sulfenylation (Scheme 4). Subsequently, adding 1 equiv. of reactant **6a** in the same pot and stirring for 20 min at ambient temperature affords the synthesis of final products. Results obtained



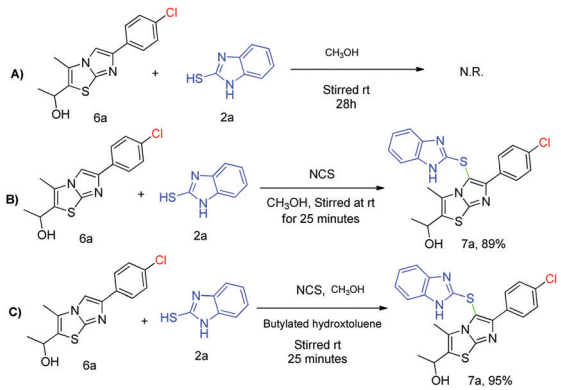
Scheme 3 Scope of substrate: variation of substituent on 2 aminothiazole[a,b]. [a]Reaction conditions: NCS (2.0 mmol) heterocyclic thiol (1.0 mmol), substituted 2-aminothiazole **4a–e** (1 mmol), CH_3OH (3 mL), reaction time (24–25 min). [b]Isolated yield.



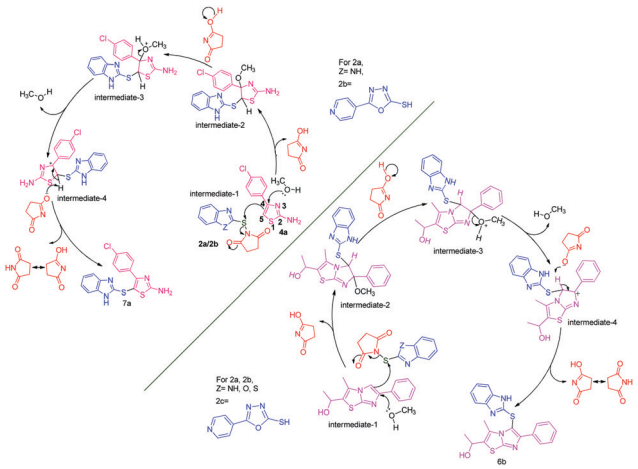
Scheme 4 Variation of substituent on imidazothiazole[a,b]. [a]Reaction conditions: NCS (2.0 mmol) heterocyclic thiol (1.0 mmol), substituted imidazothiazole **6a–e** (1 mmol), CH_3OH (3 mL), reaction time (24–25 min). [b]Isolated yield.

demonstrate that derivatives with electron-withdrawing groups on the aromatic ring at the para position provide the product with a satisfactory yield (Scheme 4), whereas with electron-donating groups such as the methyl group at the same position tend to decrease the yield of the product (Scheme 4). Electron-releasing substituents failed as exemplified by the reactant possessing the methoxy group at the same position. Variation in the heterocyclic thiol was not seen to alter the yield of the product. Interestingly, in each derivative selective sulfenylation was seen to take place at the C-5 position of imidazothiazole derivatives regardless of the pendant alcohol. Also, no derivatives were seen to give sulfenylation on an aromatic ring. The probable mechanistic path was further studied by taking other mechanistic pathways into account (Scheme 5). It came to our attention that the reaction does not proceed in absence of any catalyst or co-reagent after 28 h (Scheme 5A). The implementation of *in situ*-generated (NHTS) results decrease reaction time to 25 min, yielding 89% (Scheme 5B). When same protocol was carried out in presence of the radical quenching agent butylated hydroxtoluene BHT (2 equiv.), we were still able to get 95% yield (Scheme 5c), ruling out the possibility of free radical mechanistic path. Considering the observations of controlled experiments, optimized reaction conditions and (DFT) studies, the tentative mechanism of the reaction is given in (Scheme 6). The 4-(4-chlorophenyl)thiazol-2-amine (**4a**) derivative has been taken as the representative of all the derivatives.

The mechanistic path was studied by DFT calculations, as illustrated in (Scheme 6). The observations in Table 1 and



Scheme 5 Screening experiments.



Scheme 6 Plausible mechanistic path for the thiolation of substituted imidazothiazole and 2-aminothiazole.

Scheme 5 indicating the role of CH_3OH in the reaction is not only limited to the solvent effect but it also takes part in the mechanism as a reagent.[91–94] Initially, the reaction between (**4a**) and (NHTS) in presence of CH_3OH leads to an intermediate-1 with bond formation between C-5 of (**4a**) and -S of (NHTS). Here, methanol is found to be bonded at C-4 that induces the electronegativity of C-5 to facilitate C–S bonding. The release of succinimide is found during the formation of intermediate-2 with -H transfer from methanol. Subsequently, methanolate abstracts -H from succinimide (intermediate-3) and leaves to form intermediate-4. The disappearance of profound IR stretching frequency around 3210 cm^{-1} (Table S1, ESI†) indicates the formation of product (**5a**).

Conclusions

In summary, we have developed a metal-free, mild and selective protocol for the synthesis of novel sulfenylated 2-aminothiazoles and imidazothiazoles *via in situ*-generated (NHTS). Our study exemplifies that NHTS is acting as a co-reagent in the current procedure. The method adopted ensures chemoselectivity towards the C–H bond functionalisation in the presence of secondary alcohol in imidazothiazole, setting up the application of NHTS for the pharmaceutical and agrochemical arenas.

Conflicts of interest

There are no conflicts to declare.

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Original Article: DTP/SiO_2: An Efficient and Reusable Heterogeneous Catalyst for synthesis of Dihydropyrano[3,2-c]Chromene-3-Carbonitrile Derivatives

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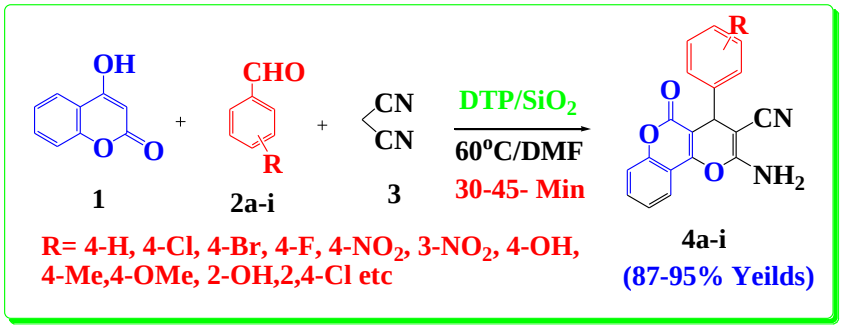
DTP/SiO_2, green synthesis, dihydropyrano[3,2-c]chromene-3-carbonitrile.

ABSTRACT

An efficient and convenient method has been developed for the synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives from one-pot multicomponent reaction between 4-hydroxy-2H-chromen-2-one. Aromatic aldehydes and malononitrile were catalyzed by DTP/SiO_2 as an efficient and reusable heterogeneous catalyst. The current method provides adavtages over reported method viz simple operational procedure, easy isolation and recyclability of the catalyst, environmental benign, reduced reaction time and superior yield.



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Introduction

Silica-supported DTP/SiO_2 is simple to prepare and shows good acidic characteristics. The acidic properties of DTP/SiO_2 can be controlled by activation temperature and has shown significant catalytic activity [1]. DTP/SiO_2 exhibits efficient heterogeneous catalytic properties for the synthesis of wide variety important organic building blocks such as α-aminophosphonate [2]. Moreover, it is successfully employed as catalyst for the many organic transformations *viz* C-H activation and functionalization of nitrogen containing aromatic heterocycles [3, 4], Fries rearrangement [5], Friedel-Crafts benzylation of anisole [6].

The pyrans are considered as an important building block for the synthesis of several natural products [7] and photochromic materials [8]. The heterocyclic entities containing pyrans ring show many medicinal and pharmacological properties and are involved in may biochemical reactions [8]. Furthermore, pyrans serve as important synthetic intermediates for the synthesis of biologically important compounds such as pyrano-pyridnes [9], poly-azanaphthalenes [10], pyrano[2-c]pyrimidines [11], and pyridin-2-ones [12]. Hence, the synthesis of hetrocyclic compounds containing pyran nucleus has attracted the attention of many synthetic and medicinal chemist. Moreover, the herteocyclic compounds containing pyrano[3,2-c]chromene nucleus is a class of important heterocycle with broad spectrum of biological activities [13] involving spasmolytic, diuretic, anti-coagulant, anti-cancer and anti-anaphylactic activity [14]. The chromene building block with fused ring system has proved to expand the biological spectrum with superior anti-bacterial profile against numerous microbes such as bacteria and fungi [15]. The fused chromene containing heterocycles has shown the excellent biological properties viz antiproliferative [16], sexpheromonal [17], mutagenicitical [18], anti-tumor [19], anti-viral [20] and CNS depressant activities [21].

There are many methods available in the literature for the synthesis of dihydropyrano[3,2-*c*]chromene compounds via one-pot multicomponent reaction (MCR) between 4-hydroxycoumarin with aldehydes and malononitriles such as $H_6P_2W_{18}O_{62}/18H_2O$ [22], sodium dodecyl sulfate (SDS) [23], DBU [24], Tetrabutylammonium bromide (TBAB) under solvent free and in aqueous condition [25], ionic liquid [26], sulfonic acid functionalized silica (SiO_2PrSO_3H) [27], poly(N,N'-dibromo-N-ethyl-benzene-1,3-disulfonamide) [PBBS] and N,N,N',N'-tetrabromobenzene-1,3-disulfonamide [TBBDA] [28], trisodium citrate [29], Biguanide-functionalized Fe_3O_4/SiO_2 magnetic nanoparticles [30], inorganic–organic hybrid magnetic nanocatalyst Fe_2O_3 [31] Ru(II) phosphine complexes [32], Silica-bonded n-propylpiperazine sodium n-propionate [33], 2-hydroxyethylammonium formate (ionic liquid) [34], bleaching earth clay [35] etc. However, these reported methods have been found to be inadequate in terms of longer reaction time, lower practical yields, ease of handling of hazardous chemicals, isolation of the product, lack of catalytic reusability etc. Taking into account the limitation of the reported methods, we can still have a scope to develop new method for the synthesis of dihydropyrano[3,2-*c*]chromene derivatives. To address the shortcomings of reported methods, herein we reported DTP/SiO_2 as efficient, recyclable heterogeneous catalysts for the synthesis of dihydropyrano[3,2-*c*]chromene derivatives.

Experimental

General

All the physical constants were recorded in an open capillary tube and were uncorrected. The reagents, chemicals and solvents used were of synthetic grades and were used as obtained. The reactions were monitored by thin layer chromatography on precoated sheets of alumina gel-G (Merk, Germany) using iodine vapours and or UV light for detection. The Infra-Red (IR) spectra were recorded on Schimadzu Spectrophotometer (KBr pellets). ^1H NMR (300MHz) and ^{13}C NMR (100 MHz) spectra

were recorded in DMSO-d6 or $CDCl_3$ using TMS an internal standard with an Avance spectrometer (Bruker, Germany). Mass spectra were determined on an EI-Schimadzu QP 2010+ GCMS system.

2.1. General procedure for the synthesis of 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives 4:

A mixture of 4-hydroxy-2H-chromen-2-one 1 (1 mol), aldehyde (2a–2n) (1.1 mol), malononitrile 3 (1.1 mmol), and DTP/SiO_2 (20 wt %) in DMF (10 mL) was heated to 60°C with stirring about 30-50 Minute (Table 2). The progress of reaction was checked by TLC. After completing the conversion of reactant into product (by TLC), the catalyst was filtered off and reaction mixture was allowed to cool at room temperature. To this cooled mixture, ice cold water (50 mL) was added and stirred mechanically for 5-10 min. The solid was separated out, filtered and recrystallized from ethanol to afford the pure products **4 a-n**.

2.1.1.Product 4a: Pale yellow powder; (purified by recrystallization with ethanol); IR (KBr) cm^{-1}: 3323, 3204, 2195, 1720, 1668, 1601, 1519, 1381, 1264, 1143, 1048, 761, 481; ^1H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 4.40 (1H, s, pyran-CH), 7.21-7.30 (5H, m, arom.), 7.36 (2H, s, NH_2), 7.40-7.48 (2H, m, arom.), 7.69 (1H, t, J = 7.2 Hz, arom.), 7.86 (1H, d, J = 7.2 Hz, arom); ^{13}C NMR (100 MHz, DMSO-d6, TMS) δ ppm; 37.1, 57.9, 103.8, 112.9, 116.6, 119.2,122.5, 124.7, 127.2, 127.7, 128.6, 133.0, 143.4, 152.2, 153.5, 158.1, 159.6.

2.1.2. Product 4b: Grayish solid; (purified by recrystallization with ethanol); IR (KBr) cm^{-1}: 3319, 3310, 3195, 2196, 1718, 1676, 1608, 1377, 1057, 954, 757, 506; ^1H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 2.21 (3H, s, CH3), 4.36 (1H, s, CH), 7.05-7.11 (4H, m, arom.), 7.34 (2H, s, NH_2), 7.39-7.47 (2H, m, arom.), 7.66 (1H, t, J = 9.0 Hz, arom.), 7.86 (1H, d, J = 9.0 Hz, arom.); ^{13}C NMR (100 MHz, DMSO-d6, TMS) δ ppm; 20.7, 36.7, 58.2, 104.2, 113.1, 116.6, 117.8, 119.3, 122.5, 124.7, 127.6, 129.1, 132.9, 136.3, 140.5, 152.2, 153.3, 158.0, 159.6.

2.1.3. Product 4c: White solid; (purified by recrystallization with ethanol); IR (KBr) cm^{-1}: 3370, 3290, 3182, 2191, 1709, 1671, 1605, 1571, 1507, 1459, 1379, 1319, 1251, 1178, 1111, 1052, 1026, 951, 834, 756, 564, 529; ; ^1H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 3.68 (3H, s, OCH3), 4.35 (1H, s, CH), 6.82 (2H, d, J = 8.4 Hz, arom.), 7.13 (2H, d, J = 8.4 Hz, arom.), 7.33 (2H, s, NH_2), 7.38-7.47 (1H, m, arom.),7.63-7.69 (1H, m, arom.), 7.84 (1H, dd, J = 7.5 Hz, J = 1.2 Hz, arom.), 7.93 (1H, d, J = 9.0 Hz, arom.); ^{13}C NMR (100 MHz, DMSO-d6, TMS) δ ppm; 36.2, 55.1, 58.4, 104.3, 114.0, 115.3, 116.6, 119.4, 122.5, 124.8, 128.8, 132.9, 133.5, 135.5, 152.2, 153.1, 158.0, 159.6, 160.5.

2.1.4. Product 4e: Light yellow colored solid; (purified by recrystallization with ethanol); IR (KBr) cm^{-1}: 3402, 3323, 3204, 2197, 1714, 1670, 1604, 1509, 1379, 1264, 1143, 1047, 761, 481; ; ^1H NMR (300 MHz, DMSO-d6 TMS) δ ppm ; 4.46 (1H, s, CH), 7.23 (2H, d, J = 8.4 Hz, arom.), 7.43-7.50 (6H, m, NH_2 + arom.), 7.68-7.72 (1H, m, arom.), 7.88 (1H, d, J = 7.2 Hz, arom.); ^{13}C NMR (100 MHz, DMSO-d6, TMS) δ ppm; 36.4, 57.7, 103.6, 113.1, 116.6, 119.1, 122.6, 124.8,128.6, 129.6, 131.7, 133.1, 142.4, 152.3, 153.6, 158.1, 159.7.

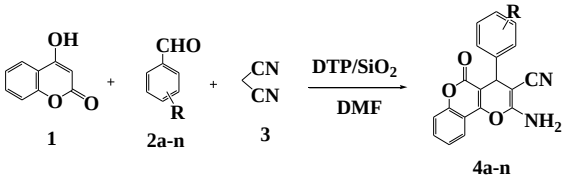
2.1.5. Product 4f: Yellow colored solid; (purified by recrystallization with ethanol); IR (KBr) cm^{-1}: 3385, 3305, 3188, 2191, 1712, 1674, 1606, 1375, 1060, 759, 510; ; ^1H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 5.12 (1H, s, CH), 7.17-7.23 (3H, m, NH_2 + arom.), 7.34 (3H, t, J = 8.7 Hz, arom.), 7.46 (4H, t, J = 10.1 Hz, arom); ^{13}C NMR (100 MHz, DMSO-d6, TMS) δ ppm; 37.0, 56.6, 116.5, 116.9, 119.5, 120.7, 124.8, 125.1, 125.8, 129.8, 130.4, 131.9, 134.5, 142.5, 150.3, 154.1, 159.0.

2.1.6. Product 4j: Yellow colored solid; (purified by recrystallization with ethanol); IR (KBr) cm^{-1}: 3390, 3212, 3179, 2197, 1662, 1575, 1465, 1409, 1260, 1227, 746, 548; ^1H NMR (300 MHz, DMSO-d6 TMS) δ ppm: 4.64 (1H, s, CH), 7.44 (2H, t, J = 7.5 Hz, arom.), 7.49-7.54 (2H, m, arom.), 7.57 (2H, s, NH_2), 7.69 (1H, t, J = 7.5 Hz, arom.), 7.87 (1H, d, J = 7.5 Hz, arom.), 8.14 (2H, d, J = 8.4 Hz, arom.); ^{13}C NMR (100 MHz, DMSO-d6, TMS) δ ppm; 22.3, 36.9, 43.9, 56.9, 102.9, 113.0, 116.7, 118.9, 122.7, 123.8, 124.8, 129.2, 133.2, 146.7, 150.8, 152.4, 154.0, 158.1, 159.6.

2.1.7. Product 4k: Yellow colored solid; (purified by recrystallization with ethanol); IR (KBr) cm^{-1}; 3382, 3235,3179, 2193, 1728, 1663, 1600, 1416, 1298, 1173, 1119, 1010, 753, 472; ^1H NMR (300 MHz, DMSO-d6 TMS) δ ppm: 4.69 (1H, s, CH), 7.42 (1H, d, J = 8.7 Hz, arom.), 7.48 (1H, d, J = 7.8 Hz, arom.), 7.52 (2H, s, NH_2), 7.59 (1H, t, J = 7.8 Hz, arom.), 7.68 (1H, dt, J = 8.0 Hz, J = 8.0 Hz, J = 1.4 Hz, arom.), 7.76 (1H, t, J = 7.8 Hz, arom.), 7.87 (1H, d, J =7.2 Hz, arom.), 8.08 (2H, d, J = 7.8 Hz, arom.), ^{13}C NMR (100 MHz, DMSO-d6, TMS) δ ppm; 22.3, 36.8, 43.9, 57.1, 103.0, 113.0, 116.7, 119.0, 122.5, 124.8, 130.2, 133.2, 134.8, 145.6, 148.0, 152.4, 154.0, 158.3, 159.7.

Result and Discussion

To pursue our work towards development of efficient methods for the synthesis of important heterocyclic compounds adopting MCRs [35], herein we became interested in developing an environmental friendly method involving use of DTP/SiO_2 as an efficient, recyclable heterogenous catalyst for the synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives through a one-pot multi-component condensation reaction of 4-hydroxyquinolin-2(1H)-one, aldehydes, and malononitrile. By a preliminary experiment, we found that this three-component condensation reaction catalyzed by DTP/SiO_2 worked very well. Hence, inspired by the preliminary experiments, herein we have reported an efficient one-pot multi-component synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano [3,2-c] chromene-3-carbonitrile derivatives in excellent yields (Scheme 1).



Scheme 1. Synthetic route of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives

Initially, we investigated the three-component condensation reaction of 4-hydroxy-2H-chromen-2-one **1**, benzaldehyde **2a**, and malononitrile **3** in the presence of various catalyst; the results are tabulated in Table 1.

Table 1. Comparison of catalytic activity of various catalysts for synthesis of pyrano[3,2-c]chromene-3-carbonitrile derivatives

Entry	Solvent	Catalyst	Yield%
1	Methanol	DTP/SiO_2	60
2	Ethanol	DTP/SiO_2	64
3	DCM	DTP/SiO_2	70
4	Acetonitrile	DTP/SiO_2	75
5	DMF	DTP/SiO_2	94
6	Water	DTP/SiO_2	N R
7	DMF	20%DTP/SiO_2	94
8	DMF	30%DTP/SiO_2	94

[a]Isolated yields

In order to optimize the reaction condition viz. catalyst loading and solvent, a model reaction was studied by varying the range of solvent including polar and non-polar solvent. In order to find out the appropriate solvent for the synthesis, the model reaction was carried out by using solvents such as methanol, ethanol, dichloromethane (DCM), acetonitrile, Dimethyl formamide (DMF). However, the DMF solvent gave the preferred pyrano[3,2-c]chromene-3-carbonitrile product in good yield (Table 1, entry 8), whereas methanol, ethanol, DCM and acetonitrile, respectively gave moderate yield (Table 1, entries 1–4). The formation of the preferred product was not observed using water as the solvent (Table 1, entry 6). This indicates that the solvent play the key role for the activity and performance of the catalyst. The above observations indicate the reaction using polar protic solvent that shows an astonishing effect on the yield of the product. Thus, with the reaction in the presence of polar

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Silica-supported sodium carbonate: an efficient heterogeneous catalyst for the synthesis of new thiazolopyrimidine derivatives

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Abstract
Herein we describe a new convenient strategy for the synthesis of substituted thiazolopyrimidines. The present approach delivers the use of silica-supported sodium carbonate (SSC) as a recyclable heterogeneous catalyst in PEG- 400 solvent. The described synthetic route offers an easy access for the synthesis of titled compounds through green chemistry protocols.

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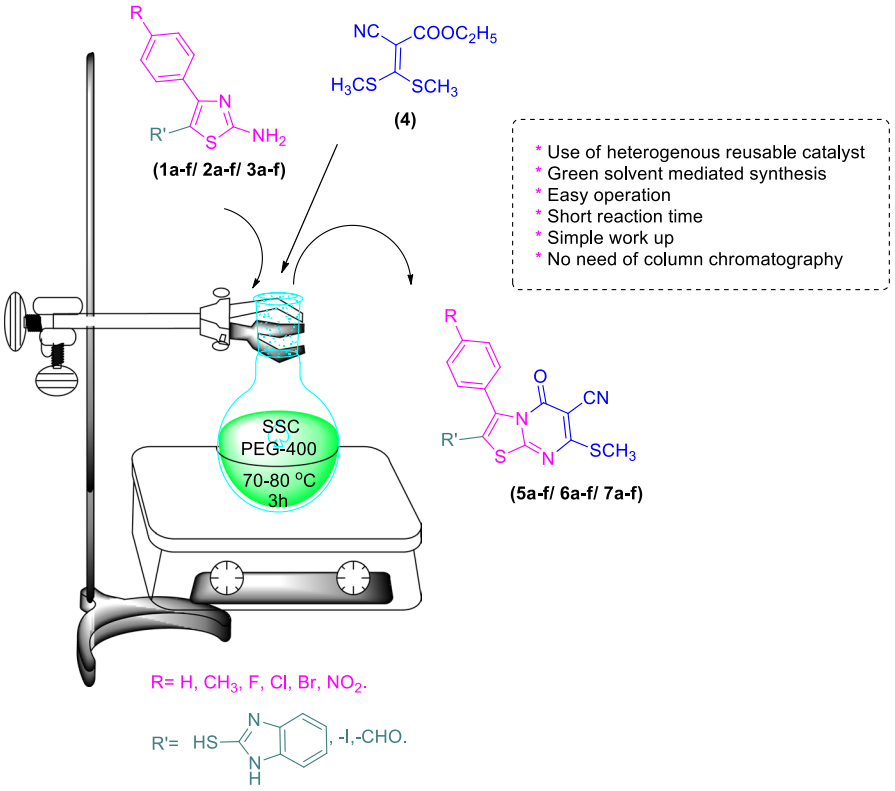
Graphic abstract



Keywords Thiazolopyrimidine · Silica-supported sodium carbonate (SSC) · PEG-400

Introduction

2-aminothiazoles and their derivatives have occupied a distinct place in the research field because of their applications in the area of pharmaceuticals such as antimicrobial [1], fungicidal [2], antiviral [3]. Amongst these, most of the 2-aminothiazoles derivatives have been substituted with diverse groups for pharmaceutical targets [4–6]. These derivatives persist for maintaining various biological systems. The pyrimidine ring is the core structure in vitamins like thiamine, riboflavin, and folic acid [7, 8]. Pyrimidine derivatives are also found to have a broad range of chemotherapeutic effects with anti-angiogenic [9], antileishmanial [10], antitubercular [11] properties. Combinations of thiazole and pyrimidine scaffold in thiazolopyrimidine are found to be active as anticancer [12, 13], antidiabetic [14], antitubercular [15], anti-inflammatory [16], anti-HIV [17], antiparkinsonian agents [18],

phosphate inhibitors [19], and acetyl cholinesterase inhibitors [20]. Several methods are reported for the synthesis of thiazolopyrimidines [21–23]. Amongst those, 2-(bis(methylthio)methylene) malononitrile and ethyl 2-cyano-3,3- bis(methylthio) acrylate are found to be common starting materials from last two decades [24, 25]. Conventional methods adopted for the synthesis mostly include anhydrous K_2CO_3 [26], and triethylamine [27–29] as a catalyst. Cyclization of heterocyclic compounds using ethyl 2-cyano-3,3- bis(methylthio)acrylate may provide a chance for the synthesis of novel hybrid molecules increasing the biological potency of the synthesized molecule [30]. Recently, Vishnu Ji Ram et al. had developed a novel approach to the synthesis of tetrahydrophenanthro[4,3-b]thiophenes utilizing ethyl 2-cyano-3,3-bis(methylthio)acrylate [31]. A. Khodairy and co-workers had also demonstrated the use of the same reagent for the synthesis of triazepin derivatives utilizing t-BuOH and triethylamine [32]. Due to this versatility, researchers are always in the search of new catalysts for these transformations [33].

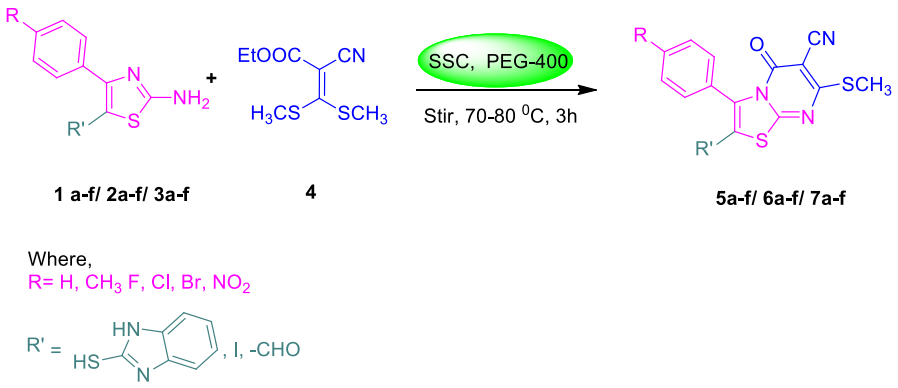
Recently researchers in organic synthesis have attracted enormous attention towards heterogeneous catalysts due to their precedence [34–37]. Heterogeneous catalyst serves several advantages over conventional homogeneous catalyst [38–40] in which most important is entire process becomes eco-friendly due to reusability of catalyst, and thus plays an excellent role in organic chemistry attributed to environmental and economic considerations [41]. Heterogeneous catalysts are also accessible on various supports, like charcoal, alumina, polymer, and silica to improve the catalytic activity [42]. It is manifest from the earlier literature that silica-supported catalysts are placed in the frontier in supported heterogeneous catalysts due to their peculiar features including no swelling, good mechanical and thermal stability, high efficiency owing to large surface area, greater selectivity, low toxicity, reusability, and ease of handling [43, 44]. Silica-supported catalyst has summoned immense attention as a green, heterogeneous, and eco-friendly catalyst for cyclization adaptation [45, 46]. Anticipating these annotations and our previous work regarding the development of eco-friendly methods for the synthesis of heterocycles [47–49], the synthesis of thiazolopyrimidine derivatives commences with cyclization of the substituted thiazole and ethyl 2-cyano-3,3- bis(methylthio)acrylate using silica-supported sodium carbonate catalyst. The present protocol emphasizes the utilization of green solvent media PEG- 400.

Result and discussion

The strategy for the synthesis of targeted compound begins with highly efficient and environmental benign heterogeneous catalyst (SSC) in PEG- 400. The (SSC) has been prepared according to the formerly reported method [50, 51].

Reaction conditions: Catalyst, 5-substituted-4-(4-substitutedphenyl)thiazol-2-amine (1a-f/2a-f/ 3a-f)) (1 mmol), ethyl 2-cyano-3,3-bis(methylthio)acrylate (4) (1 mmol), SSC (0.01 mmol), PEG- 400 (5 ml).

The 2-((1H-benzo[d]imidazol-2-yl)thio)-3-(4-substitutedphenyl)-7-(methylthio)-5-oxo-5Hthiazolo[3,2-a]pyrimidine-6-carbonitrile **(5a-f)** (Scheme 1) was obtained by (1 mmol) of 5-((1Hbenzo[d]imidazol-2-yl)thio)-4-(4-substitutedphenyl)



Scheme 1 Synthesis of substituted thiazolopyrimidine derivatives (**5a-f/6a-f/7a-f**)

thiazol-2-amine **(1a-f)** with ethyl 2-cyano-3,3- bis(methylthio)acrylate **(4)** (1 mmol) on stirring at 70–80 °C in the presence of PEG-400 and (0.01 mmol) of SSC for 3 h. Products (5a-f) were confirmed by spectral analysis.

To obtain the 3-(4-substitutedphenyl)-2-iodo-7-(methylthio)-5-oxo-5H-thiazolo[3,2- a]pyrimidine-6-carbonitrile **(6a-f)** (Scheme 1), reactant 4-(4-Substitutedphenyl)-5-iodothiazol-2- amine **(2a-f)** (1 mmol) was stirred at 70–80 °C using PEG-400 as solvent with ethyl 2-cyano3,3-bis(methylthio)acrylate **(4)** (1 mmol) with (0.01 mmol) of SSC for 3 h. The formed products (6a-f) were confirmed by spectral analysis.

Similarly, 2-amino-4-(4-substituted phenyl)thiazole-5-carbaldehyde **(3a-f)** (1 mmol) (Scheme 1) was stirred with ethyl 2-cyano-3,3-bis(methylthio)acrylate **(4)** (1 mmol) and (0.01 mmol) of SSC in PEG-400 at 70–80 °C for 3 h to form 3-(4-substituedphenyl)-2-formyl-7-(methylthio)-5-oxo-5H-thiazolo[3,2- a]pyrimidine-6-carbonitrile (7a-f). The formulated products were confirmed by spectral analysis.

Completion of the reaction through cyclization was confirmed by acceptable spectral analysis which flashes the absence of primary amine peaks in IR spectrum and recognizes the removal of both the protons during cyclization. Again, the peak of –C=O stretching at 1675 cm^{-1} indicates the presence of amide instead of ester group. In ^{1}H NMR, absence of–NH_2 and appearance of one -CH_3 group protons signal from their reputed regions proved the cyclization.

To synthesize the titled compounds (5a-f/6a-f/7a-f) quantitatively, we studied the optimization of reaction at different conditions for better yield. Initially, we carried out the reaction under catalyst-free and solvent-free condition and observed that reaction was not carried out at RT or even at higher temperature. Then, we performed the reaction without catalyst in DMF (dimethylformamide) and found 22% yield of the product at 70–80 °C. After that, we studied the reaction by using different catalysts such as triethylamine, K_2CO_3, Na_2CO_3, and SSC, in DMF as solvent. At that time, we got 42% (refluxing for 8 h), 54% (refluxing for 6 h), 58% (refluxing for 6 h), and 64% (for refluxing 6 h) yields of product, respectively (Table 1, entries 2–5). From those test results, we got to know that SSC was shown to be more

Table 1 Optimization of the catalyst for the synthesis of (**5a**)

Entry	Catalyst	Solvent	Time (Hours)	Yield (%)
1	No catalyst	DMF	12	22
2	Triethyl amine	DMF	8	42
3	K_2CO_3	DMF	6	54
4	Na_2CO_3	DMF	6	58
5	SSC	DMF	6	64

effective in terms of yield. This may be due to binding capacity and large surface area provided by the heterogeneous nature of SSC. Even though 64% yield was not satisfactory for the quantitative synthesis of the product, subsequently we shifted our attention towards solvent. We used SSC catalyst and optimized it, especially in water, ethanol, ethylene glycol, and PEG- 400 as a safe solvent to embrace green chemistry characteristics, and studied the solvent influence. We came to know that the reaction did not proceed in case of water as a solvent even after 6 h (Table 2, entry 1). Then, after we examined the reaction for remaining aforementioned solvents we found that the yield of the product increases progressively from ethanol (68%), ethylene glycol (74%), and glycerol (78%) (Table 2, entry 2–4); however, the time of reaction completion remained same, i.e. 6 h.

But when we observed the reaction in PEG- 400, we realize the sudden increase in product yield up to 89%, whereas the time for completion of reaction also reduced to 3 h (Table 2, entry 5). This may be as a result of hydrogen bonding of PEG- 400 solvent with catalyst SSC and also its phase transfer catalytic nature which results into the formation of product in proficient yield. Here we revealed a new methodology for the synthesis of thiazolopyrimidines using SSC catalyst along with PEG-400 as a solvent to get the best results in terms of yield (89%) and reaction time (3 h) and make the whole process eco-friendly.

The reusability is one of the most crucial benefits of the heterogeneous catalyst and cost-effective significances. Therefore, the recovery and reusability of the catalyst were examined. The recyclability of the catalyst was examined with the model reaction. The catalyst was recovered after the completion of the reaction by simple filtration method. The separated catalyst was dried at 60–70 °C for 8–10 h and again tested up to five more times under the same conditions. The catalyst established outstanding recyclability in all these reactions (Fig. 1), whereas the reaction times and

Table 2 Influence of the solvent for the synthesis of (**5a**)

Entry	Solvent	Catalyst	Time (Hours)	Yield (%)
1	Water	SSC	6	NR
2	Ethanol	SSC	6	68
3	Ethylene glycol	SSC	5	74
4	Glycerol	SSC	6	78
5	PEG-400	SSC	3	89

NR = No reaction

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SPECTRAL, THERMAL, XRD STUDY OF NEW LA(III), CE(III), ND(III), METAL COMPLEXES OF ASYMMETRICAL LIGAND DERIVED FROM DEHYDROACETIC ACID

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Abstract: Solid numerous colored complexes of La(III), Ce(III), Nd(III) from tetradentate Schiff bases are synthesized from o-phenylenediamine,3-Acetyl-6-methyl-pyran-2,4-dione and 5-bromo Salicylaidehyde.The structures of ligand and complexes are characterized by elemental analysis, magnetic susceptibility, thermal analysis, X-ray diffraction, ^{1}H-NMR, mass, IR,UV-visible spectra, and conductometry. TGA/DSC spectral and kinetic parameter of the complexes was observed keenly. The x-ray diffraction data proposes Monoclinic crystal system for La (III)complexes and orthorhombic for Ce (III) and Nd (III) complexes. The ligand and their metal complexes were subjected for antibacterial activity against *Escherichia coli* and *Staphylococcus aureus, Pseudomonas Aeruginosa*and antifungal activity is observed by poison plate method against *Aspergillus Niger, Aspergillus flavus, Penicilliumchrysogenum.*

Keywords: Tetradentate Schiff Base, Dehydroacticacid, Powder X-raydiffraction, Thermal analysis Antimicrobial activity.

Introduction

In this paper we are pronouncing our earlier work in the series of lanthanides of tetradentate Schiff bases formed by the reaction of o-phenylenediamine, DHA, and 5-bromo Salicylaldehyde (Fig.1). The complexes of various color, of La (III), Ce(III), and Nd(III) with this tetradentate ligands were synthesized and characterized.

Experimental

Materials

Merck was the supplier for all reagents and solvents. DHA, *o*-phenylenediamine, and 5-bromo Salicylaldehyde of AR grade were used for synthesis of ligand. AR grade metal chlorides were also used for the formation of the complexes.

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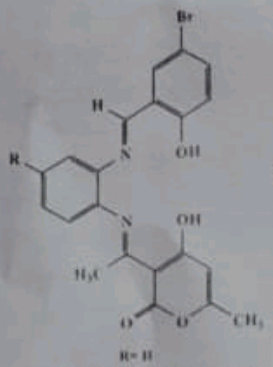
Table 5 Antifungal Screening of ligand and their metal complexes

Test Compound	Microorganisms		
	Asp. Niger	*Asp. flavus*	*Pen. chrysogenum*
L_1	-ve	-ve	-ve
L_1-La	-ve	-ve	-ve
L_1-Ce	-ve	+ve	-ve
L_1-Nd	-ve	-ve	-ve
DMSO	+ve	+ve	+ve
Griseofulvin	-ve	-ve	-ve

-ve-No growth Antifungal activity present , +ve-Growth Antifungal activity absentRG -Reduced growth



R= H

Figure 1. Structure of ligand

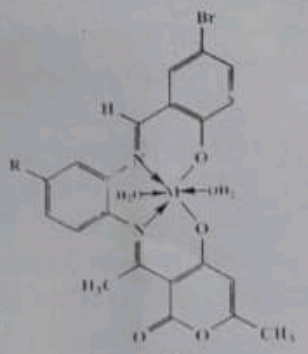


Figure 2(b)

Fig.1 The structure of the Ligand,Fig.2 b the proposed structure of the complexes, Where M=La (III), Ce (III), and Nd (III)

Conclusion

In present search we proclaiming synthesis of ligand and its transition metal complexes. Spectral study suggest that azomethine nitrogen and phenolic oxygen are involved in the coordination with metal ions (fig.1). Proposing octahedral geometry for La (III), Ce (III), Nd(III)complexes. It is concluded that the ligand is dibasic in nature and ONNO tetradentate metal complexes are biologically active and show enhanced antimicrobial activities compared to its free ligand. The x-ray diffraction data proposes Monoclinic crystal system for La (III) complexes and orthorhombic for Ce (III) and Nd (III) complexes. Thermal study predicts thermal behavior of complexes.

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