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Synthesis, spectral, and anti-microbial studies of thioiminium iodides and amine hydrochlorides

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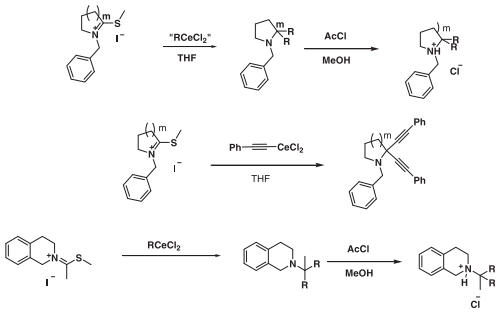
HIGHLIGHTS

- The use of simple nucleophiles results in bis and mono addition.
- The ultrasound sonication is used to prepare the organocerium reagents.
- The arrangement of protons in the amine hydrochlorides is investigated by COSY.
- The amine hydrochlorides are found to be active against some microorganisms.
- The functionalities in the molecules that cause for such activity are rationalized.

GRAPHICAL ABSTRACT

A series of germinal bis-alkyl cyclic amines and their hydrochlorides have been prepared by simple nucleophilic addition on appropriate thioiminium iodides using organocerium reagents. The amine hydrochlorides thus prepared display considerable antimicrobial activity.



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ABSTRACT

To avoid the undesired deprotonation during the addition of organolithium and organomagnesium reagents to ketones, the thioiminium salts, easily prepared from lactams and amides are converted into 2,2-disubstituted and 2-monosubstituted amines by reaction with simple nucleophiles such as organocerium and organocopper reagents. The reaction of thioiminium iodides with organocerium reagents derived by transmetalation of corresponding lithium reagents with anhydrous cerium(III) chloride has been investigated. These thioiminium iodides act as good electrophiles and accept alkylceriums towards bisaddition. The newly synthesized amines have been characterized by ^{1}H and ^{13}C NMR, IR and mass spectra. The amines have been converted into their hydrochlorides and characterized by COSY. These hydrochlorides have been subjected to antimicrobial screening with clinically isolated microorganisms, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Candida albicans*. The hydrochlorides show quite good activity against these bacteria and fungus.

Introduction

Bis addition products of thioiminium ions have been extensively studied and are reported to be done by organomagnesium and organocerium reagents [1]. Heterocycles having methylsulfonyl group and particularly cyclic amines with N-benzyl substituent possess considerable biological activity [2,3]. Thioiminium ions are prepared from lactams converted into thiolactams and reaction of them with methyl iodide. Bis alkylation is mainly dependent on nucleophilicity of organometallic reagents. For instance, we test alkylmagnesium reagents in bis-alkylation and find they are not quite nucleophilic enough to give addition products on

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thioiminium ions. Now we report that organocerium reagents are very effective for addition reactions of these salts. The preparation of thioiminium ions are shown in the scheme 1.

Experimental

All reactions were performed under nitrogen atmosphere in oven-dried flasks (120 °C) unless otherwise stated. Dry solvents for reactions were filtered through a column of dry alumina under positive pressure of argon. Solvents for flash chromatography were of technical grade and used without

purification. Other chemicals were obtained from commercial sources and used without further purifications. The reactions were monitored by TLC (analytical plates, Merck silica gel 60 F254) and visualized under UV light and/or stained with a solution of $KMnO_4$ or phosphomolibdic acid followed by heating. Flash chromatography (FC) was performed using *Baker* silica gel (0.065–0.200 mm). Melting points (m.p.) determined are not corrected. ^1H and ^{13}C NMR spectra were recorded on *Bruker Avance*-300 (^1H: 300 MHz, ^{13}C: 75.5 MHz) or *Bruker DRX*-400 (^1H: 400 MHz, ^{13}C: 100 MHz) or *Bruker Avance-III* (^1H: 400 MHz, ^{13}C: 100 MHz) spectrometers. The ^1H spectra were referred to an internal standard (TMS, 0 ppm) or to the residual ^1H of $CDCl_3$ (7.26 ppm). ^{13}C spectra were referred to residual signal of $CDCl_3$ (77.0 ppm). IR spectra were recorded on *Jasco FT-IR* 460 *plus*. Mass spectroscopy (MS) and high resolution mass spectroscopy (HRMS) analyses were performed on *Waters Micromass Autospec Q/Qstar Pulsar*.

Five bacterial cultures one gram-positive *Staphylococcus aureus*, three gram-negative namely, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Salmonella typhi* and one fungal strain namely *Candida albicans*, were used for the bioassay. All the organisms were isolated from clinical patients and obtained from K.A.P. Viswanatham Government Medical College, Tiruchirappalli, India.

The organisms were maintained on agar slopes at 4 °C and sub cultured for 24 h before use. While the bacteria strains were incubated into nutrient broth throughout 24 h, the fungal strains were incubated into Saubouraud's dextrose agar throughout 48 h.

General procedure A: synthesis of thioiminium ions in Scheme 1

Lawesson's reagent (2.02 g, 5.0 mmol) was added to a solution of the lactam (10 mmol) in dry CH_2Cl_2 (100 mL). The mixture was stirred at room temperature for 1–4 h until the starting material was consumed (TLC monitoring). The solvent was evaporated and the crude mixture was filtered on short column of silica gel (cyclohexane/EtOAc). The thiolactam (10 mmol) was suspended in dry THF (100 mL) and MeI (1.0 mL, 16 mmol) was added. The mixture was stirred at room temperature overnight. The thioiminium ion was isolated by filtration and washed with cold THF to obtain yellowish solid.

General procedure B: synthesis of gem-dialkylated amines in Scheme 2

A suspension of $CeCl_3$ (0.296 g. 1.2 mmol) in dry THF (4 mL) was soniccated at room temperature for about 30 min. The suspension was cooled down to −78 °C and the alkyllithium reagent solution (1.2 mmol) was added dropwise. The solution became pale yellow and stirring was continued for about 30 min. The thioiminium salt was added as a solid (0.3 mmol), the cooling bath was removed and the mixture was stirred for about 6 h. The dark brown suspension was treated with saturated NH_4Cl and the aqueous phases were extracted with dichloromethane (3×). The collected organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by FC (cyclohexane/*tert*-BuOMe) to afford the *gem*-dialkylated amine.

General procedure C: preparation of amine hydrochlorides in Scheme 2

The free amine was treated with HCl (generated from the addition of acetyl chloride to MeOH at 0 °C) to give the amine hydrochlorides.

Results and discussion

Synthesis of thioiminium iodides

The thioiminium iodides (**7–9**, **12** and **15**) were prepared by the action of methyl iodide on thiolactams. These thiolactams were obtained from the commercially available and easily prepared lactams (**1–3**, **10** and **13**) (Scheme 1). The lactam **1** is commercially available, whereas, **2** and **3** [4] are prepared by N-benzylation of δ-valerolactam and 6-caprolactam respectively. Conversion of lactams (**1–3**) into thiolactams enables to prepare the thioiminium ions (**7–9**) [5]. The reaction of thiolactams with methyl iodide took about 8 h to give the salts with good yield. The reaction between thiolactams and other alkyl halides like ethyl, propyl and butyl iodides was found to be slow. The lactams 1-(pyrrolidin-1-yl)ethanone (**13**) and 1-(3,4-dihydroisoquinolin-2(1H)-yl)ethanone (**10**) are prepared simply by acetylation of pyrrolidine and 1,2,3,4-tetrahydroisoquinoline respectively. They are converted into thioiminium ions (**15** and **12**). Biological activities of some of thioiminium iodides were also screened (Table 1).

Among the above thioiminium iodides, **7**, **8** and **12** are stable at room temperature for a long time in a closed container. The salt **9** is unstable at room temperature and **15** is hygroscopic in nature.

FT-IR spectra of **7–9**, **12** and **15** showed the characteristic C═N, C—S stretching frequencies that could be seen in 1600–1495 and 700–693 cm^{-1} respectively. C—C stretching appeared between 1299–1243 cm^{-1}. C—H (aromatic) stretch and C═C ring stretch (aromatic) appeared at 3085–3000 and 1590–1466 cm^{-1} respectively.

^1H NMR spectra of **7–9** showed a sharp singlet that was observed at the range of δ 5.23–4.93 ppm. This is assigned to two benzylic protons. The signal for CH_2 protons adjacent to N atom in **9** is shifted to the downfield at δ 4.22 ppm. This is the typical triplet with unexpected intensity ratio and this downfield shift is because of the adjacent positively charged nitrogen atom, which may deshield the methylene protons by the electron withdrawing nature. The CH_2 protons adjacent to positively charged nitrogen atom showed a triplet around at δ 4.17 ppm (**7**) and δ 3.75 ppm

Table 1
Antimicrobial screening of some selected compounds.

Name of the organism	Standard antibiotic	Standard zone of inhibition for selectivity (mm)	Diameter of zone of inhibition obtained (mm)												
			+ve control*	7	8	12	30	31	32	34	35	36	40	46	48
Staphylococcus aureus	Ampicillin	17	–	6	6	5	1	2	–	1	1	–	1	1	–
Salmonella typhi	Chloramphenicol	18	3	9	7	6	–	2	–	–	2	–	–	1	–
Pseudomonas aeruginosa	Gentamicin	15	9	9	8	3	1	1	1	1	4	2	1	2	3
Candida albicans	Ketoconazole	18	–	10	–	4	–	–	–	1	–	–	–	2	3
Klebsiella pneumoniae	Streptomycin	15	–	–	–	–	–	–	–	1	1	–	–	1	–

* zone of inhibition obtained (mm) for the standard antibiotics used.