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CAN-catalyzed microwave promoted reaction of indole with Betti bases under solvent-free condition and evaluation of antibacterial activity of the products

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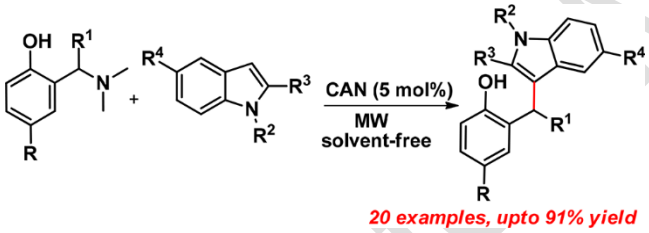
ABSTRACT

CAN-catalyzed reaction of Betti bases with indoles under microwave irradiation gives 3-(α,α-diarylmethyl)indoles. Better yield of the products, especially when one of the aryl ring is phenol were achieved. The reaction is performed in solvent-free condition. The antibacterial studies of the synthesized compounds were performed and some of the compounds showed good activity against Methicillin-resistant *Staphylococcus aureus* bacteria.

GRAPHICAL ABSTRACT



KEYWORDS: 3-(α,α-diarylmethyl)indoles, Betti base, CAN-catalyzed, microwave, solvent-free

Introduction

Ceric (IV) ammonium nitrate (CAN) is a versatile reagent in carrying out several organic reactions. CAN is extensively used as one electron oxidant in carrying out oxidation reactions.[1] This catalyst is air stable and easy to work with. The low cost and toxicity in addition to reasonably good solubility in organic solvents has made it very attractive catalyst for carrying out many

organic reactions.[2] Many carbon-carbon and carbon-heteroatom bond forming reactions are catalyzed by CAN.[3],[4] Use of CAN as catalyst in multicomponent reaction and green synthesis is reviewed by Prajapati et al.[5]

Microwave technology was used by organic chemists from the later part of 1980. Since then microwave synthesis has attracted chemists due to its faster and clean reaction over conventional heating method. The pharmaceutical industry which require more number of chemical compounds are greatly assisted by using microwave technology which allow quicker access to organic compounds. The use of microwave technology in organic chemistry is extensively reviewed in literature.[6],[7]

N-containing heterocyclic compounds are found to have several biological activities. Indole nucleus is very important moiety in many important molecules having wide medicinal applications.[8] Many alkaloids having indole as core unit have broad spectrum activities.[9] C-3 substituted indoles have found applications in several fields including perfumery, agrochemical, pharmaceutical, etc. industries. Many antifungal, antibacterial, analgesic, antipyretic, anticancer, antidiabetic compounds are found to be C-3 substituted indole derivatives.[10] When the indole nucleus substituted with various groups or attached with other heterocyclic moieties, they are found to affect the antioxidant properties of the resulting coumpounds.[11],[12] Naphthol and phenol derivatives possesses several biological activity. Most of the phenolic substances have important biological activities and are found to be the key components in the defence of plants against herbivores and pathogens.[13] Many natural phenolic compounds may prevent cancer.[14] They have strong antioxidant property and therefore, function as protective agents against many free radical mediated diseases.[15]

Result and Discussion

The bioactivity of the 3-alkylated indoles and phenols inspired us to synthesize compounds having both indole and aryl alohol moiety. Although considerable progress has been made in the synthesis of these compounds, development of efficient synthesis with mild catalyst and improved reaction condition is highly sought-after. We have observed in our previous studies that the yield of the 3-(α,α-diarylmethyl)indoles from indole Mannich base is low when the aryl alcohol moiety is phenol compared to napthol.[16] Further, reaction of the Betti base with indole under microwave irradiation catalyzed by PTSA gave us bis(indolyl)methane through denaphtholation.[17] We thus searched for an alternative method which would give better yield of the 3-(α,α-diarylmethyl)indoles having phenol component and also prevent the C-C bond cleavage. To attain a better method for the reaction, several catalysts were screened under microwave and thermal condition. We observed that various Lewis acid and organocatalysts did not afford good yield of the product. Use of Bronsted acids (e.g. HCl-2N) was also not productive. We were delighted to find that CAN in acetonitrile as solvent gave us moderate yield. To compare the solvent affect, we performed the reaction in different solvents and the results are presented in **Table 1**. However, we observed that the optimum yield was obtained when 5 mol% of CAN was used under solvent-free condition (entry 14, **Table 1**). Increase of catalyst loading did not increase the yield (entry 13, **Table 1**); however, lowering of catalyst amount decreases the product yield (entry 16, **Table 1**). Lowering of reaction time also diminished the yield of **3a** (entry 15, **Table 1**).

The affect of the amine moiety on the yield of the product was also studied and obtained best result when the amine moiety was dimethylamine rather than pyrrolidine and piperidine. In order to screen the substrate scope we have carried out reactions using several substituted phenols

and naphthols. We obtained very good yield for both the phenol and naphthol derivatives. We observed that when electron-withdrawing groups were present in the aryl ring (**R^1**) of **1**, the yield of the **3** was better (e.g., **3f**-**3g**, Scheme 2). However, presence of electron-donating groups on the phenol ring increased the yield (e.g., **3b** vs. **3c**, Scheme 2). On the other hand, 2-methylindole gave better yield of **3** than 1-methyl- and NH-indoles. The starting material **1** for the reaction can easily be prepared by the 3-component method using phenol, aldehyde and amine.[18] The mechanism for the formation of **3** is similar as described by our previous report which proceeds through the formation of quinone methide.[18] CAN helps to eliminate the amine group by coordinating its metal ion with the nitrogen of amine.

Bioactivity studies

Antibiotics are the substances that are produced by microorganisms most of which are manufactured synthetically and are used in the treatment of bacterial, fungal, parasitic, and viral infections by inhibiting their biological processes. The implementation of empiric antibiotic therapy has led to antibiotic resistance in many microbes. The major factor for the growth of antibiotic resistance is the spread of resistance strains of bacteria among the persons. Bacterial infections are treated by proper use of antibiotic but overuse or misuse of them enhanced bacterial resistance. Gram positive and gram negative bacteria can transfer antibiotic resistance gene through horizontal gene transfer or spontaneous mutations. Development of antibiotic resistance in pathogens has led to the development of synthetic drug molecules that are found to be effective against many microbes. We have thus tested our compounds against various bacteria and obtained promising result.

Antibacterial assay

The antibiotic sensitivity was done by well-diffusion method on Mueller Hinton agar medium using the specified test compounds and bacterial isolates viz. *E. coli*, *K. pneumoniae* & *Methicillin-resistant Staphylococcus aureus (MRSA)* isolated from clinical samples urine, sputum and pus respectively.[19] The compounds were dissolved in 70% DMSO (1mg/ml). DMSO was also used as the solvent control. After 18 to 24 h of incubation, the plates were examined and diameters of the zone of inhibition measured (**Figure 1**) and values were recorded as shown in **Table 2**.

The compounds showed no activity against *E. Coli* and *K. Pneumonaie* bacteria. The results indicates that 3-(α,α-diarylmethyl)indoles with various naphthol moiety have no activity against all the three bacterial stains studied. However the phenolic counterparts gave us promising results. **3a** showed good activity against the *Staphylococcus aureus* bacteria. When the methyl group was replaced by tert-butyl (e.g. **3b**) or –OMe (e. g. **3d**), the compounds lost activity against the bacteria. However substitution by –Cl group retained the activity. Substitution on the phenyl ring also affects the biological activity of the compounds. Compound **3f** with –F substitution showed highest activity followed by **3e** with –Cl, whereas compound **3g** with $–NO_2$ group showed no activity. Interestingly, when the nitrogen of indole is substituted with a methyl group (e.g. **3i**), the compound lost its activity completely. Further ring substitution on the phenol ring made the compounds **3k** and **3l** inactive against the studied bacteria. Similarly, substitution on the indole whether on five membered (e.g. **3j**) or six membered ring (e.g. **3h**) also eliminates bioactivity.

Minimum inhibitory concentration (MIC) test against MRSA (Methicillin-resistant Staphylococcus aureus)

MIC is defined as the lowest concentration of compound that was able to inhibit growth of bacteria. After overnight incubation in Luria Bertani (LB) Broth, the bacterial isolates were centrifuged at 4000 RPM for 5 min. The supernatant obtained was discarded and pellet was re-suspended in 20 ml of normal saline and re-centrifuged at 4000 rpm for 5 min. Pellet was then dissolved in 20 ml sterile normal saline for use in the MIC assay. Resazurin dye was prepared as per standard protocol.[20] In a 96 well microtitre plate, the first row of the plate was filled with 100 µL of the test compound and all the wells were filled with 100 µL of LB broth. Two fold serial dilutions were achieved transferring 100 µL from the first well to the subsequent wells such that each well has 100 µL of sample in decreasing concentration. 10 µL of resazurin dye was added to each well as an indicator. Finally 10 µL of the bacterial suspension was added to all the wells and the plate was loosely wrapped with cling film to ensure that bacteria did not become dehydrated. Each plate had two controls: i) a well with all solutions with the exception of the test compound and ii) a well with all solutions except bacterial suspension, replaced by LB Broth. The plate was incubated overnight at 37°C and then observed for any visible colour change. Colour change from purple to pink or colourless was considered as positive. The lowest concentration of the test compound at which the colour change was observed was recorded as the MIC value **Table 3**.[20]

Conclusion

In conclusion, we have developed a mild and efficient method to synthesize 3-(α,α-diarylmethyl)indoles. The main advantage of this method is that phenol derivatives could also be synthesized in higher yield than the previously reported methods. The biological activity study of the synthesized compounds was done and promising results were obtained. The antibacterial activity of the compounds were tested against clinical bacterial isolates of *Escherichia coli, Klebsiella pneumoniae & MRSA(Methicillin-resistant Staphylococcus aureus)* using *agar* well

diffusion method. The zone of inhibition ranged from a maximum of 20 mm to minimum of 13 mm against *MRSA*. However no significant activity was observed against the gram negative bacteria- *E. coli* and *K. pneumoniae.* Further MIC test was carried out for the biologically active compounds. Compound **3f** showed the most effective MIC value of 8.33µg/ml against selected isolate of *MRSA*. Thus the present work could open up new possibility for biological activity studies of this important class of compounds. Further, studies on improving the activity against other resistant bacterial and fungal stains are underway and the results would be reported soon.

Experimental

General experimental procedure for the synthesis of 3

1 (1.0 mmol), **2** (1.0 mmol) and CAN (5 mol %, 27.5 mg) were irradiated in a closed vessel inside a microwave reactor at 110°C for the specified time. The progress of the reaction was monitored by TLC. After completion of the reaction the crude mixture was purified by column chromatography using hexane/ethyl acetate as the eluent to give the desired product **3**. Representative characterization of **3a**: off white solid; Yield: 263 mg, 84 %; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.82 (d, J = 1.0 Hz, 1H), 9.19 (s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.28 – 7.15 (m, 5H), 7.11 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.76 – 6.74 (m, 2H), 6.65 – 6.64 (m, 1H), 5.95 (s, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.3, 144.4, 136.7, 130.1, 129.8, 128.7, 128.0, 127.4, 126.8 (2C), 125.8, 124.2, 121.1, 119.0, 118.3, 117.9, 115.0, 111.5, 40.5, 20.5; MS: m/z = 314.2 $[M + H]^+$.

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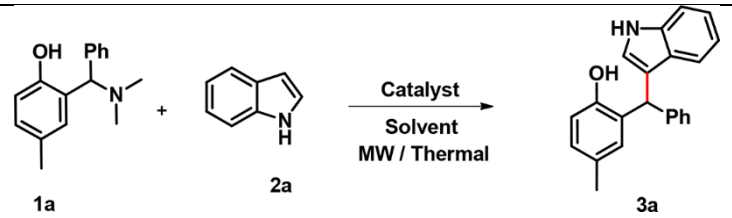
Table 1. Optimization of the reaction condition.[a]



1a 2a 3a

Entry	Catalyst (mol %)	Solvent	Time (min), MW/[Thermal]	Yield, 3a (%)[b], MW/[Thermal]
1	–	–	10 [180]	trace [NR][c]
2	–	CH_3CN	10 [180]	trace [NR]
3	AcOH (10)	CH_3CN	10 [180]	25 [trace]
4	*p*-TsOH (10)	CH_3CN	10 [180]	33 [45]
5	TFA (10)	CH_3CN	10 [180]	30 [37]
6	Thiourea (20)	CH_3CN	10 [180]	trace [NR]
7	$FeCl_3.6H_2O$ (10)	CH_3CN	10 [180]	20 [NR]
8	PNBA (10)[d]	CH_3CN	10 [180]	15 [NR]
9	CAN (10)	CH_3CN	10 [180]	67 [25]
10	CAN (10)	DMF	10 [180]	25 [18]
11	CAN (10)	Toluene	10 [180]	56 [41]
12	CAN (10)	EtOH	10 [180]	28 [15]
13	CAN (10)	–	8 [90]	84 [51]
14	**CAN (5)**	–	**8 [90]**	**84 [43]**
15	CAN (5)	–	7 [60]	76 [40]
16	CAN (3)	–	8 [90]	50 [29]

17	Silica gel (10)	–	10 [180]	NR [NR]
18	H_3BO_3 (10)	–	10 [180]	trace [NR]
19	HCl-2N (10)	–	10 [180]	44 [26]
20	LiCl (10)	–	10 [180]	trace [NR]
21	$CuCl_2$ (10)	–	10 [180]	trace [NR]

[a]Unless otherwise mentioned, all the reactions were performed by using **1a** (1.0 mmol, 241mg), **2a** (1.0 mmol, 117 mg). 110˚C was maintained for all the reactions under microwave condition. In thermal condition, reactions were carried out under reflux. [b]Products were purified by column chromatography and yields are of isolated products. [c]NR: no reaction. [d]*p*-Nitro benzoic acid.

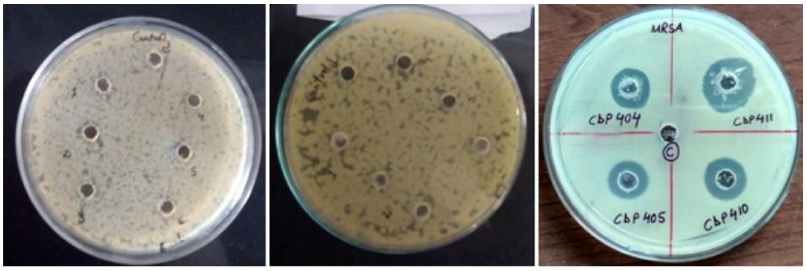
Table 2. Calculation of zone size.

Compound code	Organism	Zone size (mm)
3f	MRSA	20
3e	MRSA	16
3a	MRSA	14
3c	MRSA	13

Table 3. Calculation for MIC mean value and standard error.

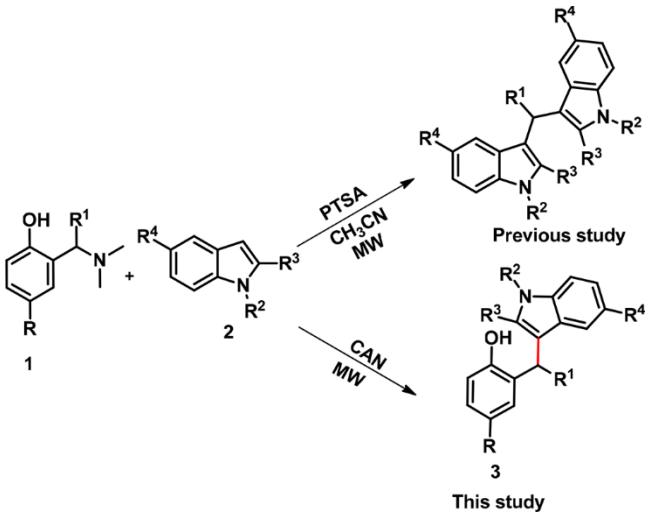
Drug (µg/ml)	Organism	Mean value ± standard error
3f	MRSA	8.33 ± 0
3e	MRSA	25 ± 0
3a	MRSA	25± 0
3c	MRSA	12.5 ± 0

Figure 1. Antibacterial test against bacterial strains. **a**: *E. coli* (–ve); **b**: *K. pneumonia* (–ve); **c**: MRSA (+ve).



(a) (b) (c)

Scheme 1. Reaction of Betti bases with indoles.



Scheme 2. Substrate scope for the synthesis of **3**. Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), CAN (5 mol %, 27.5 mg) at 110°C under microwave irradiation. Products were purified by column chromatography using silica gel (100-200 mesh) and yields are for the isolated products.