INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

CERIC (IV) AMMONIUM NITRATE CATALYZED HIGHLY EFFICIENT SYNTHESIS OF 3-AMINOINDAZOLE AND THEIR ANTIBACTERIAL SCREENING

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ABSTRACT

Ceric (IV) ammonium nitrate (CAN) catalyzed condensation of benzonitrile and hydrazine for the synthesis of 3-aminoindazole. CAN is commercially available, nontoxic, inexpensive eco-friendly and high reactivity. Use of EtOH-H_2O as a solvent and the reaction is carried out under ultrasound irradiation. The compound **3c** was investigated in-vitro against Gram +ve and Gram –ve bacteria at different concentrations and compared with standard drug ciprofloxacin.

Keywords: 3-Aminoindazole, Ceric (IV) ammonium nitrate (CAN), Ultrasound, Antibacterial.

INTRODUCTION

Indazole ring is a subject of our research work[1]. Indazole exhibit a variety of biological such as anti-inflammatory, anti-tumor, anti-HIV, anti-cancer, anti-platelet, and serotonin 5-HT3 receptor antagonist activities[2].3-Aminoindazoles which are valuable templates for medicinal chemistry. Thus they have attracted the attention of synthetic community. Several method have been published for the synthesis of 3-aminoindazole the methods have several drawback is the use of costly reagents and catalyst, organic solvents, harsh conditions and thus have limited scope[3-7].

Here our interest is to synthesize 3-aminoindazole using ceric (IV) ammonium nitrate (CAN) as a catalyst which is commercially available, inexpensive and nontoxic. CAN is used effectively as catalyst for different reaction like 1,3-dipolar cycloaddition, thiocynation, 1,4-addition and nitration[8-13]. In continuation to our previous work on ultrasound irradiated synthesis which is important technique in synthetic organic chemistry. It has been used as an important energy source for the organic reactions. Which consist of simple experimental procedure, highly selective and clean reaction[14-16].

EXPERIMENTAL SECTION

Procedure for Optimization of reaction conditions for the synthesis of 3-aminoindazole.

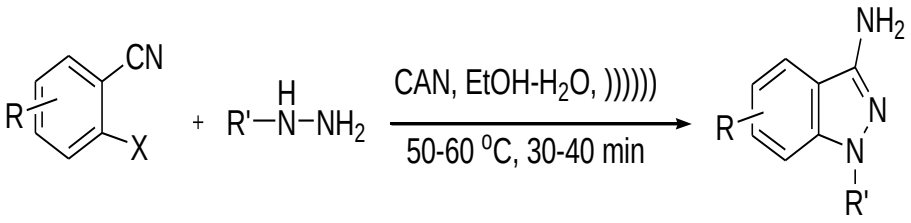
The model reaction is a condensation between benzonitrile **1c** (1.0 mmol) and hydrazine **2c** (1.2 mmol) (Scheme). The reaction which is condensation reaction catalyzed by ceric (IV) ammonium nitrate (CAN) and optimization using different mol percentage of catalyst and using different solvent at different concentration and the reaction was carried out under ultrasound irradiation. The results obtained are given in **Table 1**.Using (CAN) (10 mol %) EtOH-H_2O (2:2) (entry 9) at 50-60 ^oC

for 35 min gave excellent yield as compared to other. And further derivatives of 3-aminoindazole have been synthesized using (CAN) (10 mol %) EtOH-H_2O (2:2) under ultrasound irradiation.

Table 1: Optimizing the reaction conditions[a]

Entry	CAN mol (%)	Solvent	Time (min)	Yield (%)[b]
1	-	-	80	5
2	5	MeCN	60	40
3	10	MeCN	60	58
4	5	Toluene	70	53
5	10	Toluene	70	60
6	5	EtOH	60	68
7	10	EtOH	60	76
8	5	EtOH-H_2O (2:2)	35	80
9	10	EtOH-H_2O (2:2)	35	93
10	15	EtOH-H_2O (2:2)	35	86

[a]Benzonitrile (1.0 mmol), hydrazine (1.2 mmol), solvent and CAN
[b]Isolated Yields



(1a-h) **(2a-h)** **(3a-h)**

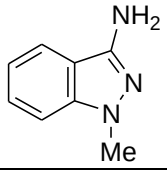
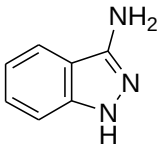
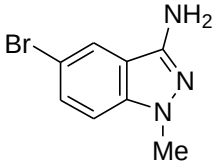
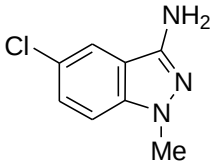
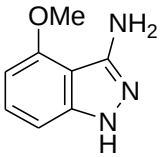
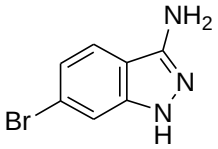
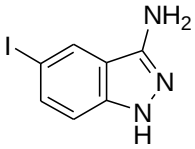
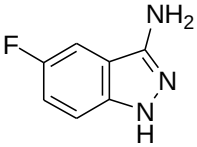
Where,

R = H, Br, Cl, OMe, I, F. R' = Me, H

X = F, Cl

Scheme. CAN catalyzed synthesis of 3-aminoindazole under ultrasound irradiation

Table 2: CAN catalyzed synthesis of 3-aminoindazole under ultrasound irradiation (3a-3h)

Comp.	R	R'	product	m.p (°C)	Yield (%)[a]
3a	H	Me		95-97	90
3b	H	H		150 -152	87
3c	5-Br	Me		133-135	93
3d	5-Cl	Me		130-132	89
3e	6-OMe	H		116-120	90
3f	4-Br	H		171-174	95
3g	5-I	H		177-179	93
3h	5-F	H		165-167	90

[a]Isolated Yields

Procedure for the synthesis 3-aminoindazole (**3a-h**)

A mixture of benzonitrile (**1a-h**) (1.0 mmol), hydrazine (**2**) (1.2 mmol) and (CAN) (10 mol %) in solvent EtOH-H_2O (2:2) and the reaction mixture was kept in the ultrasonic bath and was irradiated at 50-60°C for about 30-40 min. (the progress of reaction was monitored by TLC at different interval) separately as indicated in (**Table 2**). After the reaction was completed the reaction mass was poured on crushed ice. The obtained solid was filtered, washed with water and dried. The crude compound was crystallized using DMF-Ethanol.

Compound **3c**: Yield 93%; light yellow solid; mp 133-135℃. FTIR Model RZX (Perkin Elmer) cm^{-1}: 3426 (N-H str., -Amine), 1544 (C=N str., Indazolyl), 1342 (C-N str.), 553 (C-Br str., Ar-Br); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 3H, $-CH_3$), 5.41 (s, 2H, Amine), 7.24 (d, 1H, Ar-H), 7.33 (d, 1H, Ar-H), 7.93 (s, 1H, Ar-H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 34.55, 109.01, 110.34, 115.75, 122.88,

128.62, 139.59, 147.69 ppm;MS (ESI, m/z): calcd for $C_8H_8BrN_3$ (M + H^+) 224.9902; found: 225.9969

ANTIBACTERIAL ACTIVITY

The procedure was repeated as give in our previous published work [14-16]. Here compound 3-amino-5-bromo-1H-methyl-1H-indazole **3c** was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, Staphylococcus aureus and Bacillus subtilis and two gram negative strains, Escherichia coli and Pseudomonas aeruginosa. Ciprofloxacin was used as standard drug. The results obtained are given in **Table 3.**

RESULT AND DISCUSSION

Our interest in developing new eco-friendly methods for the synthesis of different heterocyclic reactions. Here we have performed A cyclocondensation reaction of benzonitrile (**1a-h**) (1.0 mmol) and hydrazine (**2a-h**) (1.2 mmol) to give substituted 3-aminoindazole the reacton is catalyzed by ceric (IV) ammonium nitrate (CAN).The catalyst ceric (IV) ammonium nitrate (CAN) is commercially available and was used (**scheme**).The optimization of the reaction is done using different solvents and also solvent free for model reaction which was carried out under ultrasound irradiation. The results were summarized in **Table 1**. Here good yields was obtained by using (CAN) (10 mol %) EtOH-H_2O (2:2) (entry 9) at 50-60 ^oC for 35 min. And thus the reaction was optimized and the method was used for further synthesis derivatives and the results obtained are given in **Table 2**.

The compound **3c** 3-amino-5-bromo-1H-methyl-1H-indazole was screened for in-vitro antimicrobial activity using agar disc-diffusion method against two gram positive bacterial strains, *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative strains, *Escherichia coli* and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug and the data obtained from antibacterial study is given in **Table 3** which indicates that the test compound 1-benzyl-3-hydroxy-1H-indazole **3c** showed antibacterial activity against Gram positive bacteria, *S.aureus* and *B.subtilis* it moderate activity against *S.aureus* no activity against *B.subtilis.* In case of gram negative bacteria, 3-amino-5-bromo-1H-methyl-1H-indazole **3c** showed moderate activity against *E.coli* and it is inactive against *P.aeruginosa* at all 4 concentrations. On the basis of data it is clear that 3-amino-5-bromo-1H-methyl-1H-indazole and its derivatives show moderate antibacterial activity.

Table 3: Antibacterial activity of 3c

Sr. No.	Conc. µg/mL	Zone of inhibition in mm							
		Gram +ve				Gram -ve			
		3b							
		Pathogen – Staphylococcus aureus		Pathogen – Bacillus subtilis		Pathogen – Escherichia Coli		Pathogen – Pseudomonas aeruginosa	
		Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
1	125	-	-	-	-	-	-	-	-
2	250	10	12	-	-	-	-	-	-
3	500	19	17	-	-	-	-	-	-
4	1000	24	21	-	-	8	8	-	-
Standard Ciprofloxacin									
1	125	31	31	27	27	26	26	27	27
2	250	35	36	29	29	28	28	32	32
3	500	40	41	30	31	29	31	36	34
4	1000	44	45	32	33	30	33	38	39

CONCLUSION

In conclusion, we have developed a simple and highly efficient method for the synthesis 3-aminoindazole and their derivatives using ceric (IV) ammonium nitrate (CAN) which commercially available, nontoxic and inexpensive. The reaction is performed in EtOH-H_2O (2:2) gave better as compared to other solvents under ultrasound irradiation. Thus the method is clean and efficient method. Antibacterial screening of **3c** compound was found to give moderate activity against selected strains. Further studies on the biological activities of the products and application of this methodology to other interesting 3-aminoindazole derivatives are underway in our laboratory.

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