Synthesis of some Novel 2-Substituted-N-Aryl-Benzoxazole-5-Carboxamides using Cobalt Dipyridine Dichloride as a Catalyst

M. Sarangapani[a*], D. Sridhar [b], M. Arjun[b], M. Adharvana Chari[c]

a) University College of Pharmaceutical Sciences, Kakatiya University, Warangal, India.
b) Department of Chemistry, Kakatiya University, Warangal, India, 506009.
c) Department of Chemistry, Kyung Hee University, South Korea.
drmac_s@yahoo.com

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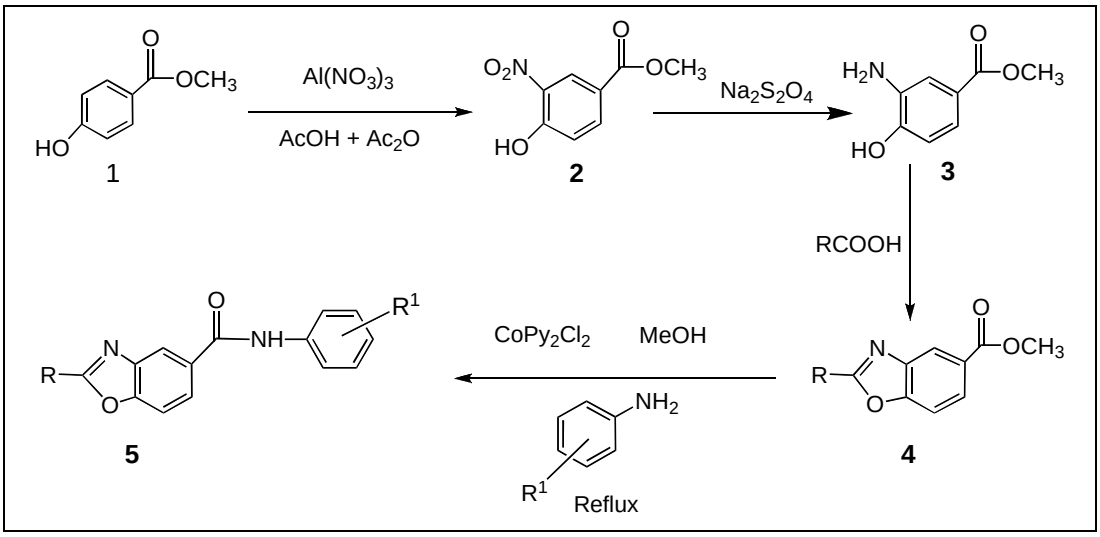

An efficient synthesis of some novel 2-substituted-*N*-aryl-benzoxazole-5-carboxamides from 2-substituted – 5-carbomethoxy benzoxazole on treatment with different substituted anilines promoted by cobalt dipyridine dichloride as a catalyst is described. This new approach has the advantage of excellent yields (90%) and short reaction times 1-2 h.

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INTRODUCTION

Benzoxazole compounds are an important class of heterocyclic compounds having anti-inflammatory [1-2], anticancer [3], and antimicrobial [4-5] activities. Benzoxazoles possess a wide range of pharmacological activities. Benzoxazoles containing an amide moiety at position 5 are not known so far. In order to get more potent compounds by combining biodynamic moieties, it is planned to synthesize some novel benzoxazole derivatives containing amides.

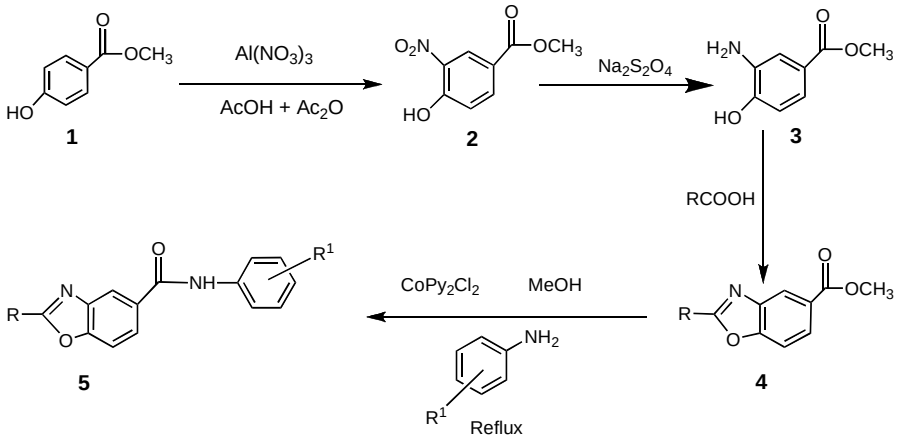
The amide moiety is an important building unit [6-7] and it is present as a key in many important natural products and man-made compounds. The practical application of this method has been limited for a number of reasons. Ester aminolysis sometimes requires harsh conditions of high temperature and extended reaction periods or the use of strong alkali metal catalysts [8-10] conditions that are not amenable to molecules bearing sensitive functional groups.

In recent years, several synthetic procedures for direct conversion of esters to amides is normally conducted under stringent conditions employing reagents [11] such as sodium methoxide, lithium aluminum hydride, sodium hydride, sodium metal, butyl lithium, potassium amide, Grignard reagents, silicon tetrachloride, boron tribromide and 2-pyridone, although their broader utility has not been established. The direct synthesis of amides by the reaction of the appropriate amine and either an acid chloride or anhydride is a well-known organic synthetic procedure. Amides and some substituted amides from primary aliphatic amines can be prepared by direct aminolysis. In general aromatic amines will not undergo this conversion. The use of a trace of sodium methoxide as a catalyst for the ammonolysis of esters is well known.

In view of the recent surge in the use of different catalysts, we wish to report a simple, convenient and efficient method for the preparation of 2-substitued-*N*-arylbenzoxazol-5-carboxamides, utilizing cobalt dipyridine dichloride [12] as catalyst. This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety and pollution. This catalyst is used for a variety of organic transformations, which is non-volatile, non-explosive, easy to handle, and thermally robust. Enhanced reaction rates and improved selectivity was obtained in the presence of this catalyst. We wish to

explore the synthesis of 2-substitued-*N*-arylbenzoxazole-5-carboxamides utilizing cobalt dipyridine dichloride as catalyst (Scheme 1).

The 2-substituted-*N*-aryl-benzoxazole-5-carboxamides **5** have been prepared by refluxing the mixture of 2-substitued-5-carbomethoxy benzoxazole **4** and substituted



RESULTS AND DISCUSSION

The treatment of 2-substituted-5-carbomethoxy benzoxazole with different substituted anilines in the presence of cobalt dipyridine dichloride causes the formation of 2-substituted-*N*-aryl-benzoxazole-5-carboxamides up to 90% yield. The crude products were purified either by recrystallization from *n*-hexane or by silicagel column chromatography. All the products were characterized by IR, ^{1}H NMR (Table I and II) and mass spectral analysis. The reactions of various substituted anilines with 2-substituted-5-carbomethoxy benzoxazole in the presence of cobalt dipyridine dichloride is superior in terms of yields and reaction rates and the results are presented in the Table III.

anilines under water bath for 50 - 120 minutes by using cobalt dipyridine dichloride as a metal catalyst. The reaction mixture was cooled, poured into crushed ice and neutralized with dilute HCl. The solid thus obtained was collected by filtration, washed with water and recrystallized from methanol to obtain the title compounds. The structures of compounds **5** are confirmed by their spectroscopic (IR, ^{1}H NMR and Mass) and analytical data.

For example, IR spectrum in KBr of the compound **5k** showed absorbance frequencies (cm^{-1}): at 3095 (N-H), 1716 (C=O), 1593 (C=N). ^{1}H-NMR spectrum (DMSO-d^6) of the compounds exhibited proton signals (δ ppm) at: 2.1 (s, 3H, CH_3) 6.8-9.2 (m, 7H, Ar-H),10.8 (s, 1H, N-H) Mass spectrum showed its molecular ion $(M+1)^+$ at m/z 287.

Table I

IR spectral data (KBr) 2-Substituted-N-aryl-benzoxazole-5-carboxamides.

Compound	R	Ar	N-H	ν_{max} in cm^{-1}	
				C=O	C=N
5a	-H	C_6H_5	3402.6	1706.1	1610.1
5b	-CH_3	C_6H_5	3416.2	1706.0	1597.2
5c	-C_2H_5	C_6H_5	3405.4	1708.1	1603.0
5d	-H	*p*-Cl	3422.0	1696.0	1616.0
5e	-CH_3	*p*-Cl	3095.9	1715.9	1592.6

Table II

^{1}H NMR spectral data of 2-substituted-*N*-aryl-benzoxazole-5-carboxamides.

Compound	R	Ar	^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm)
5a	H	C_6H_5	7.0 -10.8(10H Ar-H, including NH).
5b	CH_3	C_6H_5	2.29 (s, 3H, CH_3), 7.0-10.1 (9H, Ar-H), 9.91 (s, 1H (NH)
5d	H	*p*-Cl	7.0-10.95 (9H including NH)
5e	CH_3	*p*-Cl	2.21(s, 3H, CH_3), 7.0-10.8 (8H, Ar-H, including NH)

We have carried out cobalt dipyridine dichloride catalyzed synthesis of amides from esters in an efficient manner and this report happens to be first of its kind to achieve the products without any undesired products and the reaction is very efficient and completed in short reaction time. Usually, the amide formation from esters is carried out in presence of strong bases, like t-BuOK. But we have used cobalt dipyridine dichloride as a simple metal catalyst to achieve the good result.

Infrared spectral data of some compounds were presented in the Table I. NMR spectral data of the compounds were presented in the Table II, The physical, analytical and elemental analysis data of compounds are given in Table III.

N-aryl-benzoxazole-5-carboxamides from 2-substituted-5-carbomethoxy benzoxazole by the treatment of different substituted anilines promoted by cobalt dipyridine dichloride as a catalyst. Present methodology offers very attractive features such as reduced reaction times, higher yields and economic viability of the catalyst, when compared with conventional method as well as with other catalysts, which will have wide scope in organic synthesis. The simple procedure makes this method economic, benign and a waste-free chemical process for the synthesis of 2-substituted-*N*-aryl-benzoxazole-5-carboxamides of biological importance. The operational simplicity of the procedure is also

Table – III

Physical data of 2-substituted-*N*-aryl-benzoxazole-5-carboxamides.

Compd.	R	R^1	m.p (^OC)	Yield (%)	Mol. Formula	Time (min)	Elemental analysis % Found (calcd)		
							C	H	N
5a	H	H	156	80	$C_{14}H_{10}N_2O_2$	55	70.50 (70.58)	4.20 (4.20)	11.71 (11.76)
5b	CH_3	H	161	82	$C_{15}H_{12}N_2O_2$	50	71.40 (71.42)	4.70 (4.76)	11.07 (11.11)
5c	C_2H_5	H	174	83	$C_{16}H_{14}N_2O_2$	50	72.12 (72.18)	5.24 (5.26)	10.50 (10.52)
5d	H	p-CH_3	165	79	$C_{15}H_{12}N_2O_2$	75	71.38 (71.42)	4.70 (4.76)	11.10 (11.11)
5e	CH_3	p-CH_3	170	81	$C_{16}H_{14}N_2O_2$	60	72.10 (72.18)	5.20 (5.26)	10.48 (10.52)
5f	C_2H_5	p-CH_3	171	83	$C_{17}H_{16}N_2O_2$	90	72.81 (72.85)	5.68 (5.71)	10.00 (10.00)
5g	H	p-OCH_3	148	76	$C_{15}H_{12}N_2O_3$	80	67.10 (67.16)	4.42 (4.48)	10.40 (10.44)
5h	CH_3	p-OCH_3	155	90	$C_{16}H_{14}N_2O_3$	80	68.01 (68.08)	4.90 (4.96)	9.90 (9.93)
5i	C_2H_5	p-OCH_3	159	81	$C_{17}H_{15}N_2O_3$	75	69.05 (69.15)	5.00 (5.08)	9.44 (9.49)
5j	H	p-Cl	160	77	$C_{14}H_9ClN_2O_2$	75	61.71 (61.76)	3.29 (3.30)	10.20 (10.29)
5k	CH_3	p-Cl	164	79	$C_{15}H_{11}ClN_2O_2$	80	62.90 (62.93)	3.80 (3.84)	9.73 (9.79)
5l	C_2H_5	p-Cl	171	76	$C_{16}H_{13}ClN_2O_2$	100	64.00 (64.00)	4.30 (4.33)	9.30 (9.33)
5m	H	p-NO_2	154	81	$C_{14}H_9N_3O_4$	90	59.50 (59.60)	3.15 (3.17)	14.80 (14.84)
5n	CH_3	p-NO_2	160	85	$C_{15}H_{11}N_3O_4$	90	60.55 (60.60)	3.70 (3.70)	14.00 (14.14)
5o	C_2H_5	p-NO_2	164	80	$C_{16}H_{12}N_3O_4$	90	61.78 (61.93)	3.80 (3.87)	13.50 (13.54)
5p	H	$NHNH_2$	138	80	$C_{14}H_{11}N_4O_2$	120	62.80 (62.92)	4.00 (4.11)	20.90 (20.97)
5q	CH_3	$NHNH_2$	142	81	$C_{15}H_{13}N_4O_2$	120	64.00 (64.05)	4.50 (4.62)	19.80 (19.92)
5r	C_2H_5	$NHNH_2$	147	77	$C_{16}H_{15}N_4O_2$	120	64.95 (65.08)	5.00 (5.08)	18.90 (18.98)

CONCLUSION

We have developed a simple, convenient and effective method for facile synthesis of 2-substituted-*N*-aryl-benzoxazole-5-carboxamides from 2-substituted-5-carbomethoxy benzoxazole by the treatment of different substituted anilines promoted by cobalt dipyridine dichloride as a catalyst. Present methodology offers very attractive features such as reduced reaction times, higher yields and economic viability of the catalyst, when compared with conventional method as well as with other catalysts, which will have wide scope in organic synthesis. The simple procedure makes this method economic, benign and a waste-free chemical process for the synthesis of 2-substituted-*N*-aryl-benzoxazole-5-carboxamides of biological importance. The operational simplicity of the procedure is also attractive. To our knowledge, this is first report of an efficient general method for the synthesis of 2-substituted-*N*-aryl-benzoxazol-5-carboxamides by using a simple metal catalyst.

EXPERIMENTAL

All melting points were determined in open capillaries. The purity of the compounds was ascertained by TLC on silica gel G plates. The IR spectra were taken in KBr on a Perkin Elmer spectrophotometer. PMR spectra were recorded on a 300 MHz NMR spectrometer in DMSO- d^6. Mass spectra were recorded using LC triple quadrupole mass spectrometer (Micromass, Manchester, UK).

General experimental procedure. The 2-substituted-5-carbomethoxy benzoxazoles [5], in turn have been prepared from 4-carbomethoxy-2-aminophenol by condensation with aliphatic acids *viz*. formic acid, acetic acid and propionic acid and characterized by spectral data. The 4-carbomethoxy-2-aminophenol required for the purpose has been prepared from methyl-*p*-hydroxybenzoate by *o*-nitration with aluminum nitrate in a mixture of acetic acid-acetic anhydride and subsequent reduction with sodium dithionite, in aqueous alcohol (50%).

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