Research Article

Unprecedented Lewis Acid Catalyzed One-Pot, Three-Component Synthesis and Evaluation of Bioactive Property of 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2,5-dione

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Accepted on: 20-05-2015; **Finalized on:** 31-10-2015.

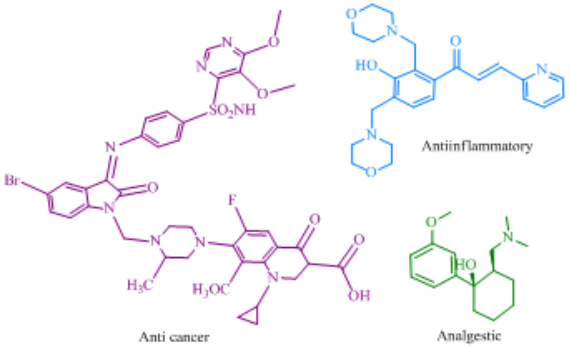
ABSTRACT

Secondary amine core activation has been achieved via intermediate of 2,5-dioxo-1-(2-oxoindolin-3-ylidene)pyrrolidin-1-ium generated from Mannich adducts of isatin and primary amine. The method has been successfully applied for a facile and efficient synthesis of a number 1-(2-oxo-3-(2-phenylhydrazinyl)indolin-3-yl) pyrrolidine-2,5-diones. 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2,5-diones have been found as core structure of AChE inhibition studiesproducts.

Keywords: indoline-2,3-dione, secondary amide, $RNHNH_2$ and AChEI.

INTRODUCTION

The synthesis of indoline-2,3-dione and functionalization of secondary amide rings with an indoline-2,3-dione group is still an important synthetic challenge in natural product organic chemistry[1] and organic synthesis[2]. Amides, polyamides and spirooxindole derivatives have been found as a key component of many synthesis of alkaloids[3], drug in biologically active[4] and pharmaceutical compounds[5] (fig 1). Isatin (2,3-dioxindole) is an endogenous compound with a long history and wide range of pharmacological actions[6]. The enlargement of novel multicomponent reactions (MCRs) and domino reactions are of interest for chemists because of high atom economy[7], their convergent character, synthesis of complex molecules[8], and simple procedures[9]. Here, for the diversity in favor of synthesis of complex molecules, it is required to change readily available materials to the target compounds via multibond formation in a simple operation[10]. Furthermore, The synthetic flexibility of indoline-2,3-dione and its derivative have led to the extensive use of this compound in synthetic organic chemistry[11]. Surprisingly, However, the corresponding nitrogen analogues 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione, have received little attention despite their potential utility as ligands for design as well as asymmetric catalysts[12].

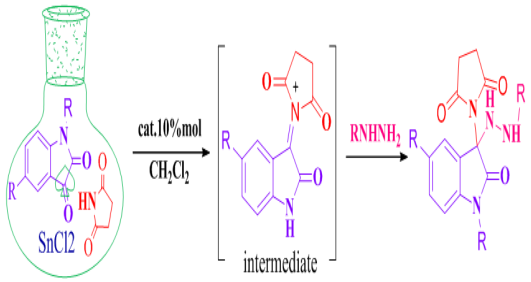


Recently, click chemistry has been emerged as a fast and efficient method for the synthesis of novel diverse chemical entities and the generation of various C-C bond forming reactions[13]. A number of synthetic routes have been developed for the preparation of these structural frameworks. Here we report the synthesis of1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione significant value of this reaction is that it provides an alternative efficient method for the preparation of ketones or aldehydes (Mannich bases), which are particularly versatile synthetic intermediates and find great use in medicinal chemistry[14]. Moreover, our search through the literature reveals that no work has been done on the condensation of imide with indoline 2,5--dione and phenyl hydrazine.(Scheme 1).

MATERIALS AND METHODS

An oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with the $SnCl_4$(22 mg, 0.03 mmol). The tube was closed with a septum, evacuated, and backfilled with argon. To this mixture was added distilled solvent DCM (2 mL); then the mixture was stirred for 30 min at room temperature.: indoline-2,3-dione (0.3 mmol), Secondary amide (0.45 mmol) and $RNHNH_2$were added. The reaction mixture was stirred at room temperature and monitored by TLC until the indolie-2,3-dione was fully consumed. The reaction mixture was passed through a pad of silica gel and washed with ethyl acetate. Several drops of the solution were collected and concentrated for the 1H NMR to determine the ratio. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethylacetate) to give the corresponding 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione as white solids : 133.7 mg (95%), Rf = 0.65 (petroleum ether/ethylacetate, 5:1); mp 169 ^{0}C; [R]25D þ242.4 (c 0.5, CH2Cl2);^{1}H NMR(500MHz, CDCl3) δ 2.57 (s, 4H), 6.86 (s,1H), 6.93-7.52 (m, 5H),11.06(s,2H); ^{13}CNMR(500MHz,CDCl3) δ 179.40, 163.38, 145.18,

144.70, 134.40, 128.13, 122.54, 115.73, 111.14,40.03, 29.58, ; IR (KBr) ν 1786, 1734, 1698cm-1; HRMS (EI) calcd for $C_{29}H_{25}NO_3$ [M] Þ 336.73, found 338.38.



RESULTS AND DISCUSSION

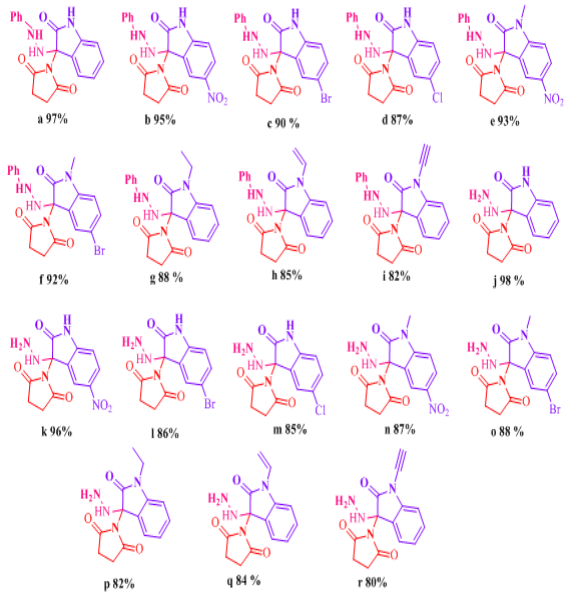
A wide variety of other Lewis acids were also examined for this reaction, with the 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione in entry 5 of Table 1 to be a model substrate, and it was found that many of them could act as promoter to give good to excellent product yields in short time (Table 1). Of all the efficient Lewis acids investigated, $SnCl_4$ gave the best result, while $AlCl_3$ was found to be too reactive to afford high yield.

Table 1: Effective Lewis Acids for the Mannich base of 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2,5-diones

Entry	Lewis acid	Yield (%)	Time (hrs)
1	$AlCl_3$	40	13
2	$ZnCl_2$	54	16
3	$Sn(OTf)_2$	50	16
4	BF_3Et_2O	62	10
5	$SnCl_4$	97	07
6	SmI_2	39	14
7	ZnI_2	32	16
8	$TiCl_4$	62	11
9	$Sc(OTf)_3$	34	16
10	$ZrCl_4$	16	12

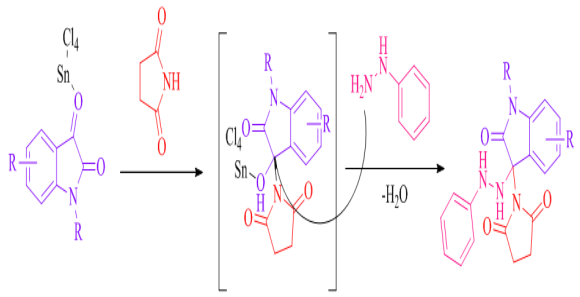
In our initial studies, we examined the reaction of imide with indoline 2,5-dione imine (1.2 equiv to imine) in the presence of Lewis acid in dichloromethane (Scheme 1)[15]. The reaction without water gave only Mannich adduct[16] even when various Lewis acids were used (Table 1). We also tried to trap the Mannich-type base **a** by the reaction in the presence of $SnCl_4$ for 7hrs, but only the mixture of Mannich adduct **a** and the indoline 2,5-dione imine was detected in the 1H NMR spectrum of the crude products. Fortunately, the use of water[17] and AlCl3 (10mol%) as a Lewis acid afforded the corresponding Mannich-type base **a** in 40% yield after 13 h at room temperature (entry 1). Surprisingly, the use of $Sn(OTf)_2$ and $Sc(OTf)_3$ and water also afforded **a** in 50% and 34 % yield (entry 3& 9), but attempts to use other Lewis acids such as $ZnCl_2$ or $TiCl_4$ with water gave only less 54 & 62 % products (entry 2 & 8). The reaction with BF_3Et_2O and water gave both desilylated product **a** and Mannich-type base **a** in a ratio of (15 mol%) by NMR analysis. We also tried to use a catalytic amount of ZnI_2(5 mol %) with water, but Mannich adduct **a** and a small amount of **a** were detected. The reaction of pure **a** with 10 mol% of $ZrCl_2$ in dichloromethane at room temperature completely gave Mannich adduct **a**[18].

A variety of alternative 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione ligands were investigated, and the indoline-2,3-dione substituted variant delivered the Mannich adduct with the highest selectivity of 82-97%. 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione ligands were also evaluated; however, their performance offered no advantages. Higher selectivity is achieved with the tridentate 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione ligands & we speculated that all the ligands might also generate a selective catalyst. Pleasingly, a reaction incorporating ligands delivered the required adduct in 97% yields. Reactions employing lower catalyst loadings resulted in significantly reduced selectivity's.



A reaction employing only Lewis acids, in the absence of any chiral ligand was used as a control to establish the inherent Mannich base of the process. Then we explored the scope of the imine components .An imines generated from indoline -2,5- dione provided the Mannich adducts with similarly high levels of yield and selectivity to the parent system (entries a-r). In general, functionalized imines are excellent substrates for the reaction, with examples of electron-donating and -withdrawing groups, and a number of halo-substituted examples all performing well. The successful use of all isatin imines demonstrates that secondary imide can be successfully employed. The indoline 2,5-dione derived imine provides a potentially useful *indoline* derivative. The methodology is limited to aromatic imines; addition of imide **1** to the indoline 2,5- dione imine generated from primary amine proceeded smoothly Mannich adduct in 98% yields. In all cases the Mannich product was obtained as the major

one[19]. This selectivity is opposite to that observed of by the addition of imide **1** to the corresponding indoline 2,5-dione and presumably originates from the primary amine group of the imines forcing coordination of the Lewis acid to the imine substituent. Control experiments established that they are constant throughout the reaction Mannich adduct (Scheme 1).



The reactions described here may be rationalized by invoking the mechanistic postulate of earlier workers[10b]. In an initial event, oxindole substituted secondary amine reacts with primary amine to form 1-(2-oxo-3-(2-phenylhydrazinyl)indolin-3-yl)pyrrolidine-2,5-diones which on deprotonation yield the 2,5-dioxo-1-(2-oxoindolin-3-ylidene)pyrrolidin-1-ium. The 2,5-dioxo-1-(2-oxoindolin-3-ylidene)pyrrolidin-1-ium undergo to yield the 1-(2-oxo-3-(2-phenylhydrazinyl)indolin-3-yl)pyrrolidine-2,5-diones as shown in scheme 1. It should be noted that the stereochemical outcome is important because the resulting stereocenters is similar to that of natural product core structures (Figure 1). The positive charge is most unstabilized at the qutnary carbon as it is attached to electron withdrawing groups *viz.* iastin and amide. Formation of the same product from isatin suggest that the reaction proceeds through a common intermediate. Removal of proton from the methylene carbon results formation of the ylide **I** which undergo resonance and through a stable products are formed.

AChE inhibition studies

All the 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione**a–r** were evaluated for their AChE inhibitory activity according to Ellmann's method[20] on AChE from electric eel using commercial Donepezil HCl as the reference standard. The results given in **Table 2** clearly show that most of the 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione **a** exhibit moderate to low inhibitory activity towards AChE with IC_{50} value ranging from 1.24–48.28 µmol/L.

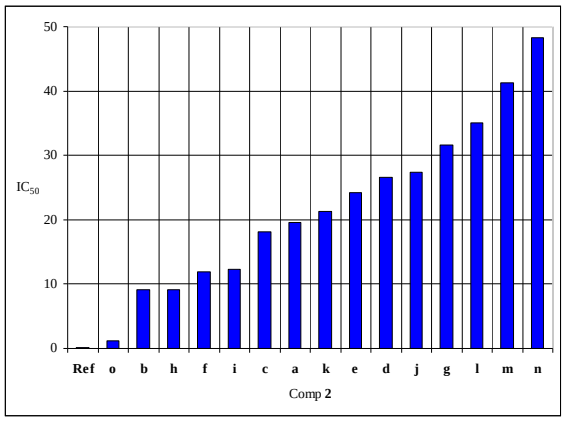
Three compounds **2b**, **2h** and **2o** show IC_{50} values of less than 10µM, whereas compounds **2f** and **2j** show IC_{50} values of less than 15µM. Two compounds **2a** and **2c** show IC_{50} values of less than 20µM and other compounds in this series were found to exhibit much less AChE inhibitory activity. Among the indole derivatives screened, compound **2o** was found to be most active AChE inhibitor with IC_{50} value of 1.24 µM. It is evident that the potency is related to the substitution in the aryl ring of (*E*)-1-(1*H*-indol-3-yl)-3-arylprop-2-en-1-ones.

Further, from **Figure1** it can be seen that the indole derivatives with halogen substituted phenyl rings are much less potent than the others. However, when compared to the standard drug all the compounds were less potent.

Table 2: AChE inhibitory activity of **1**

Comp 2	Ar	AChE Inhibition (IC_{50} ±SD)[a] µmol/L)
A	$C_{18}H_{16}N_4O_3$	19.62±0.1
b	$C_{18}H_{15}ClN_4O_3$	9.16±0.1
c	$C_{18}H_{15}BrN_4O_3$	18.11±0.1
d	$C_{18}H_{15}N_5O_5$	26.62±0.1
e	$C_{19}H_{17}N_5O_5$	24.16±0.1
f	$C_{19}H_{17}BrN_4O_3$	11.86±0.1
g	$C_{20}H_{20}N_4O_3$	31.60±0.1
h	$C_{20}H_{18}N_4O_3$	9.16±0.1
i	$C_{20}H_{16}N_4O_3$	12.24±0.1
j	$C_{12}H_{12}N_4O_3$	27.34± 0.01
k	$C_{12}H_{11}ClN_4O_3$	21.28±0.1
l	$C_{12}H_{11}N_5O_5$	35.11±0.1
m	$C_{12}H_{11}BrN_4O_3$	41.30± 0.01
n	$C_{13}H_{13}N_5O_5$	48.28±0.1
O	$C_{13}H_{13}BrN_4O_3$	-
p	$C_{14}H_{16}N_4O_3$	-
q	$C_{14}H_{14}N_4O_3$	-
r	$C_{14}H_{12}N_4O_3$	-

[a] Data are means standard deviation of duplicate independent experiments.



CONCLUSION

In summary, we have developed the Lewis acid system for synthesis of the Mannich-type bases having a terminal 1-(2-oxo-3-(2-phenylhydrazinyl) indolin-3-yl) pyrrolidine-2, 5-dione. On the basis of the proposed mechanism, carbon-nitrogen carbon bond addition containing a tertiary or quaternary carbon was achieved efficiently in the reaction.

We are currently investigating the application of the Lewis acid system, and the results will be reported shortly.

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Source of Support: Nil, **Conflict of Interest:** None.