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Synthesis of 3-acyl, methylene and epoxy substituted isoindolinone derivatives via the ortho-lithiation/cyclization procedures of aromatic imines with carbon monoxide

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ABSTRACT

A simple and convenient one-pot synthesis of 3-acyl, methylene and epoxy isoindolinone derivatives via the reaction of *o*-lithiated aromatic imines with carbon monoxide followed with acyl chlorides or $PhCO(CH_2)_nBr$ (n = 1 or 3) under mild reaction conditions has been developed. Preliminary *in vitro* tests for fungicidal activity of these isoindolinone derivatives indicated that most of them exhibit good fungicidal activity against *Sclerotinia sclerotiorum*.

1. Introduction

The isoindolinone skeleton has been found to present in numerous natural products and synthetic pharmaceuticals with a wide range of biological activities (Fig. 1).[1] For example, pagoclone shows anxiolytic activity,[2] indoprofen is a non-steroidal antiinflammatory drug,[3] and BMCI shows Kv1.5 activity.[1a] On the other hand, simple isoindolinones are versatile synthetic intermediates, and have been used as building blocks in various organic transformations to form important and more complex organic molecules.[4] Therefore, a variety of synthetic approaches to isoindolinones have been developed in the literature,[5] which are generally summed up in eight synthetic methods[6] or two categories.[7] The first category is based on phthalimides[8] or phthalimidines[9] as the starting materials. The second one is the construction of the lactam ring through cyclization reactions of various functionalized aromatic compounds, such as the amination reaction of 2-halomethyl[1b] or 2-acylbenzoate ester,[1c] 2-carboxybenzaldehyde[1a,10] and 2-alkynylbenzaldehyde,[11] as well as the *o*-lithiation/cyclization of benzamides.[6,12] In consideration of the structural diversity and the structure-activity relationship of isoindolinones, other synthetic approaches have been explored in recent years. Transition metal-catalyzed carbonylation[13] and C–H functionalization,[14] Diels–Alder[15] and inverse-electron demand Diels–Alder,[16] aza-Wittig[17] and radical cyclization[18] reactions as well as organocatalytic reactions[10a,19] have been used to build the fundamental isoindolinone skeleton. In spite of all these achievements, the substrates were not readily available in many of abovementioned cases, which were usually obtained by multistep reactions. Thus, the development of new efficient synthetic methods for isoindolinone derivatives from simple and readily available starting materials is highly desirable. Our recent investigations showed that isoindolinone derivatives were easily obtained by the reaction of *o*-lithiated aromatic imines with carbon monoxide, followed with alkyl halides under mild conditions.[20] As an extension of this work, herein we report the synthesis of 3-acyl, methylene and epoxy substituted isoindolinone derivatives through similar reactions, employing acyl chloride and $PhCO(CH_2)_nBr$ (n = 1 or 3) as the electrophiles instead of alkyl halides.

2. Results and discussion

2.1. Synthesis of 3-acyl and methylene substituted isoindolinones

Previous work has demonstrated that reaction of *o*-lithiated

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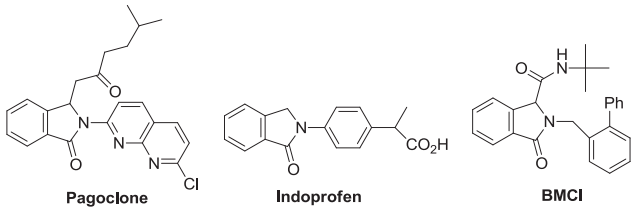
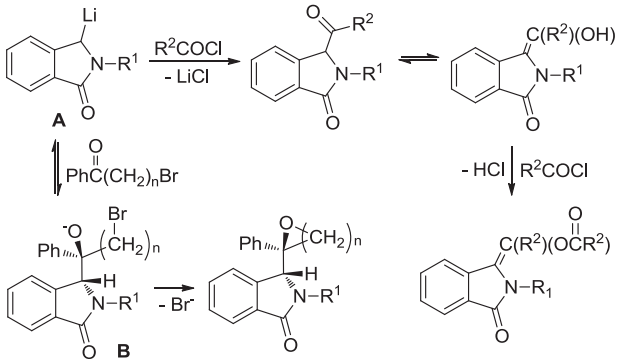


Fig. 1. Representative isoindolinone derivatives with bioactivity.

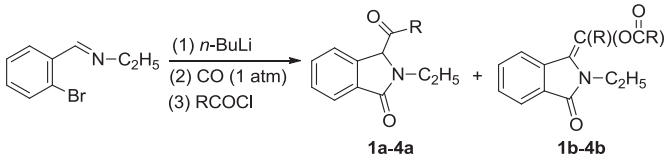
aromatic imines with carbon monoxide underwent a cyclization process to form a carbanion intermediate **A** at the 3-position of isoindolinone (Scheme 1).[20,21] We found that in situ treatment of this intermediate with one equivalent of acyl chlorides afforded 3-acyl isoindolinones (**1a**–**4a**) and 3-methylene isoindolinones (**1b**–**4b**) (Table 1, entries 1–4) when an ethyl group was attached to the nitrogen atom. The formation of the methylene isoindolinone derivatives was greatly influenced by the steric hindrance of the substituents on the nitrogen atom (Table 2, entries 1–21). With the increase of the steric hindrance of the substituents, no similar methylene isoindolinone derivatives were isolated, and the yields of 3-acyl isoindolinones were improved evidently (Table 2, entries 1–11). Moreover, even the bulky 2,6-dimethylphenyl group on the nitrogen atom was tolerable, while the corresponding 3-acyl isoindolinones were also obtained in good yields (Table 2, entries 17 and 18). On the other hand, the properties of the substituents at acyl chlorides had relatively little effect on the formation of 3-acyl isoindolinones when the N-substituent was simple aliphatic group. For example, 2-*tert*-butyl-3-ferrocenylformylisoindolin-1-one (**15**) could be obtained in an excellent yield upon *N*-*tert*-butyl-2-bromobenzaldimine as the starting material, and ferrocenecarbonyl chloride as the final electrophile (Table 2, entry 11). However, bulky electrophiles such as ferrocenecarbonyl chloride might impair the reaction when the N-substituent was rigid, such as in the case of 2,6-$Me_2C_6H_3$ (Table 2, entry 21) in which the protonated product[20] of the intermediate **A** (*ca.* 20%) was obtained together with **25**, and the repulsion between substituents could not be alleviated by rotation or compression of the substituent. In addition, pyrrolo[3,4-*b*]pyridine-7-ones (**26** and **27**) were obtained together with some other byproducts of unknown structures when the substrate was expanded to 2-bromo-3-pyridinecarboxaldimine (Table 2, entries 22 and 23). The yields were relatively low compared with those of **11** and **13** probably because the corresponding acyl lithium intermediate partially resonated to pyridyl nitrogen anion instead of similar pyridyl substituted intermediated **A**,[20] and led to other competing reactions.

The formation of **1b**–**4b** should originate from the enolization



Scheme 1. Formation pathways of 3-acyl, methylene and epoxy substituted isoindolinones.

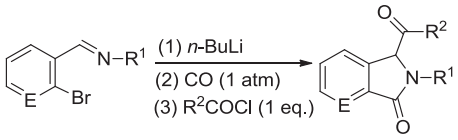
Table 1
Synthesis of 3-acyl and methylene substituted isoindolinones.



Entry	R	Isolated yield (%)	
1	Me	**1a** (50)	**1b** (15)
2	Ph	**2a** (28)	**2b** (35)
3	*p*-FC_6H_4	**3a** (27)	**3b** (53)
4	*n*-Pr	**4a** (49)	**4b** (24)
5[a]	Me	**1a** (73)	**1b** (7)
6[a]	Ph	**2a** (38)	**2b** (45)
7[a]	*n*-Pr	**4a** (74)	-

[a] Two equivalents of acyl chlorides were used.

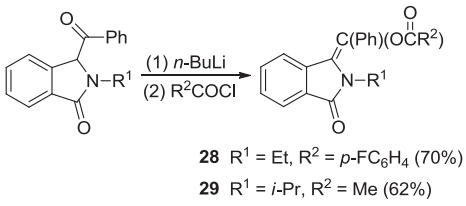
Table 2
Synthesis of 3-acyl isoindolinones.



Entry	Comp.	E	R^1	R^2	Yield (%)[a]
1	**5**	CH	Et	Ferrocenyl	48
2	**6**	CH	*i*-Pr	Me	71
3	**7**	CH	*i*-Pr	*n*-Pr	75
4	**8**	CH	*i*-Pr	Ph	73
5	**9**	CH	*i*-Pr	*p*-FC_6H_4	67
6	**10**	CH	*i*-Pr	Ferrocenyl	85
7	**11**	CH	*t*-Bu	Me	89
8	**12**	CH	*t*-Bu	*n*-Pr	94
9	**13**	CH	*t*-Bu	Ph	73
10	**14**	CH	*t*-Bu	*p*-FC_6H_4	94
11	**15**	CH	*t*-Bu	Ferrocenyl	94
12	**16**	CH	*Cyclo*-C_6H_{11}	Me	71
13	**17**	CH	*Cyclo*-C_6H_{11}	*n*-Pr	87
14	**18**	CH	*Cyclo*-C_6H_{11}	Ph	88
15	**19**	CH	*Cyclo*-C_6H_{11}	*p*-FC_6H_4	71
16	**20**	CH	*Cyclo*-C_6H_{11}	Ferrocenyl	58
17	**21**	CH	2,6-$Me_2C_6H_3$	Me	74
18	**22**	CH	2,6-$Me_2C_6H_3$	*n*-Pr	75
19	**23**	CH	2,6-$Me_2C_6H_3$	Ph	55
20	**24**	CH	2,6-$Me_2C_6H_3$	*p*-FC_6H_4	46
21	**25**	CH	2,6-$Me_2C_6H_3$	Ferrocenyl	22
22	**26**	N	*t*-Bu	Me	43
23	**27**	N	*t*-Bu	Ph	39

[a] Isolated yields.

and subsequent esterification reaction of **1a**–**4a** (Scheme 1), which was supported by treatment of **2a** or **8** with a base and followed



Scheme 2. Reaction of 3-acyl isoindolinones.