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An Expeditious Synthesis of *N*-Functionalized Isoindolinones. Application to the Synthesis of Biologically Active Compounds

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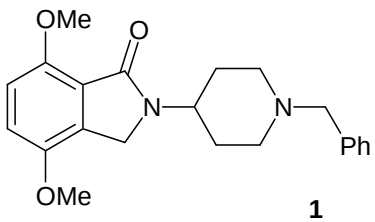
Introduction

The isoindolinone ring system has featured in recent years as a desirable synthetic target since it represents the core unit of a wide range of synthetic and naturally occurring bioactive molecules [1]. Within this family of 6,5-fused heterobicyclic compounds, model compounds functionalized on the lactam nitrogen occupy a place of choice as witnessed by a great number of recent patents emphasizing the biological potential of the piperidinyl derivatives **1** (psychoses treatment) [2], **2** (sigma receptor ligand) [3],



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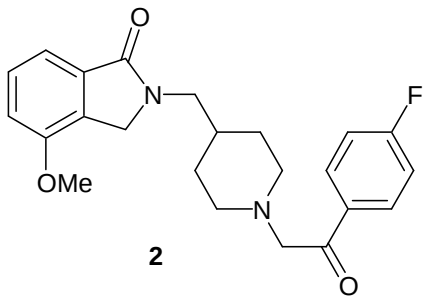

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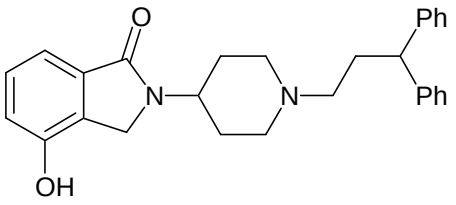
3 (microsomal triglyceride transfer protein inhibitor) [4],and of the anilinoethyl derivative **4** (inflammation and allergy inhibitor) [5].



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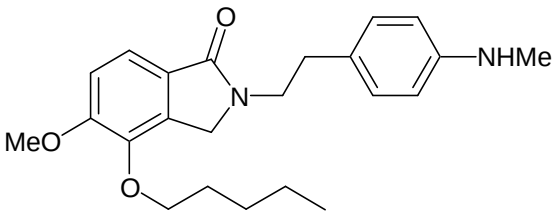

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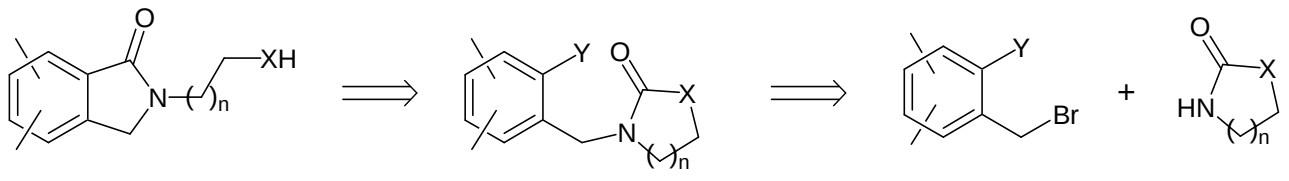
Organic chemists have at their disposal a great number of synthetic methods for the preparation of substituted isoindolinones but their applicability is quite insufficient because of restrictions in the choice of substituants namely in their nature, their number and above all their position [6]. They are notably plagued by difficulties associated with the presence of diverse functional groups connected to the lactam nitrogen.

Results and Discussion

Herein we wish to delineate a tactically and conceptually new synthetic approach to a variety of diversely N-functionalized isoindolinones. Our strategy is based upon the exploitation of the Parham cyclization process that hinges upon aromatic lithiation and subsequent reaction of the so formed aryllithiated species with an internal electrophile [7]. Application of this concept to the elaboration of five-membered lactams are scarce [8] and furthermore utilization of carbamates as internal electrophiles has been confined thus far to acyclic systems [8a, 9].

1. Retrosynthetic analysis

We reasoned that interception of the aryl lithiated species derived from compounds **6** by an oxazolidinone or an oxazinone, a thiazolidinone or an imidazolidinone ring system would provide the potential for direct access to isoindolinones **5** with the concomitant connection of the hydroxyl, thio or aminoalkyl chain respectively on the lactam nitrogen.

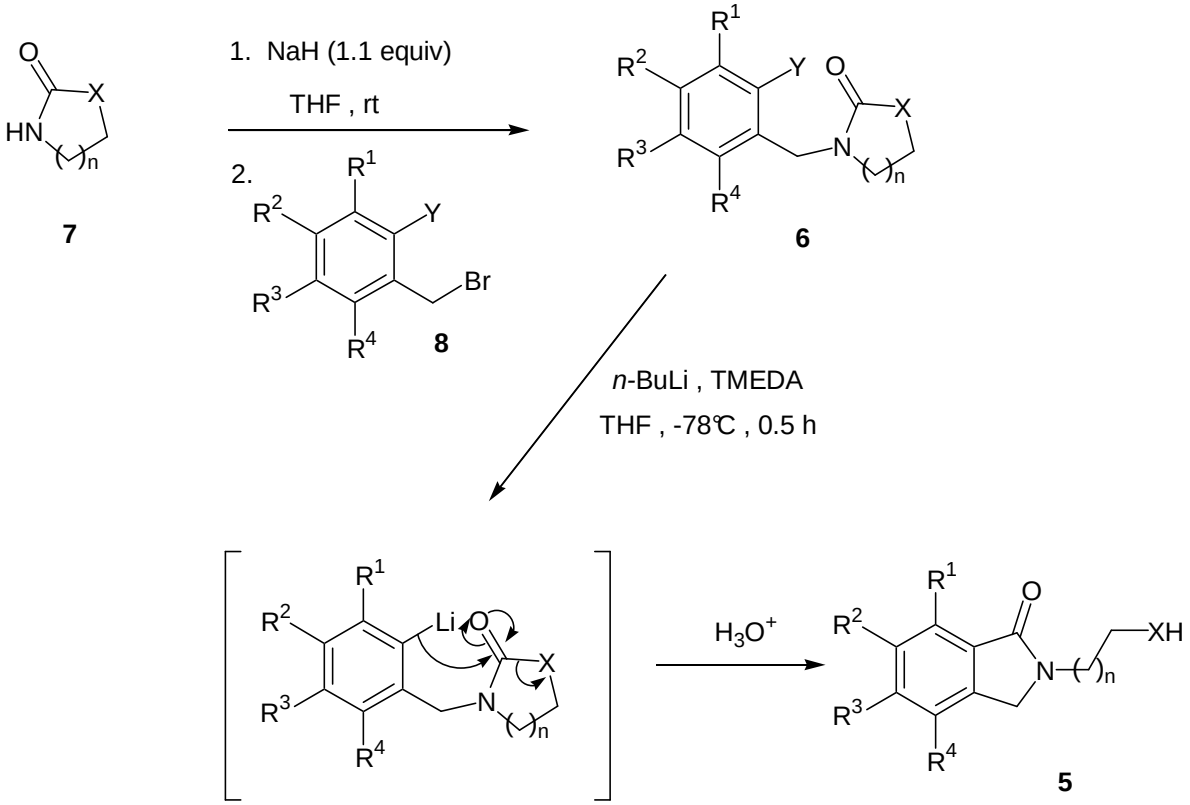


5 **6** **8** **7**

X = O, S, NR Y = Br, I

(Retrosynthetic Scheme).

2. Synthesis and anionic cyclization of the parent models



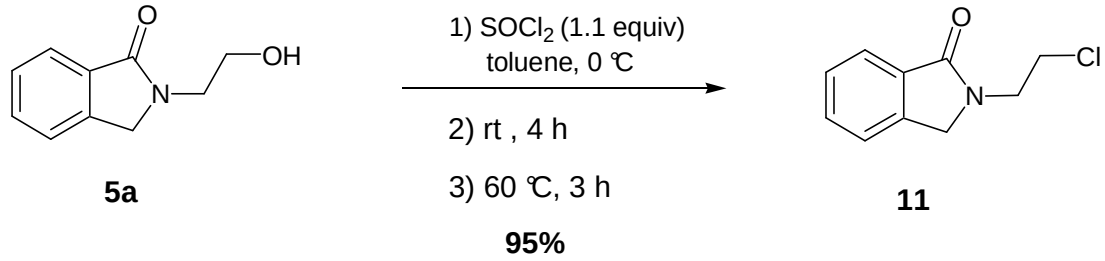
6	Y	5	X	n	R^1	R^2	R^3	R^4	Yield (%)
a	Br	**a**	O	1	H	H	H	H	71
b	Br	**b**	O	1	H	H	OMe	OMe	74
c	Br	**c**	O	1	OMe	OMe	H	H	74
d	Br	**d**	O	1	OMe	OMe	OMe	H	80
e	Br	**e**	O	2	H	OMe	OMe	H	79
f	Br	**f**	O	2	H	H	OMe	OMe	77
g	Br	**g**	O	2	H	H	OMe	H	70
h	Br	**h**	S	1	H	OMe	OMe	H	72
i	Br	**i**	S	1	H	H	OMe	OMe	76
j	I	**j**	N-Bn	1	H	OMe	OMe	H	54

3. Application to the synthesis of two pharmacologically active compounds

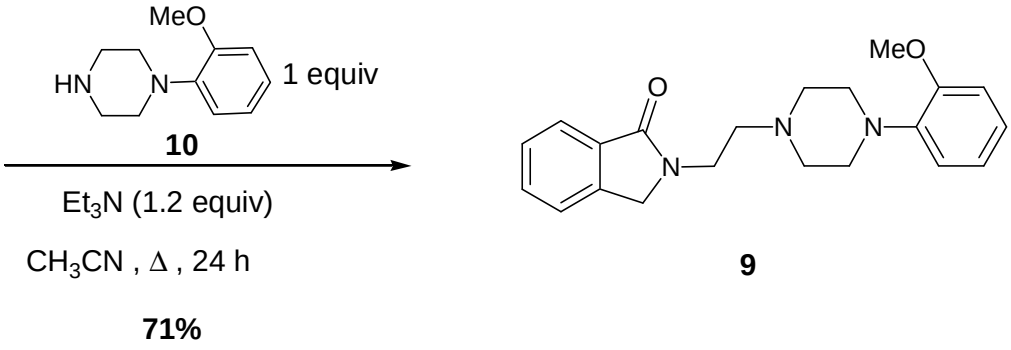
The versatility and the potentiality of the process have been emphasized by the synthesis of two highly functionalized compounds endowed with pharmacological properties.

3.1. Synthesis of 2-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-2,3-dihydro-1*H*-isoindol-1-one **(9)**

The 2-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-2,3-dihydro-1*H*-isoindol-1-one (**9**) has been shown to display very high *in vitro* binding affinity for 5-HT_{1A} receptors [10]. This compound has been readily assembled by coupling the piperazine derivative **10** with the *N*-chloroalkylisoindolinone **11** which was easily obtainable from the corresponding hydroxyl derivative **5a** synthesized according to the precedently reported procedure.



5a **11**



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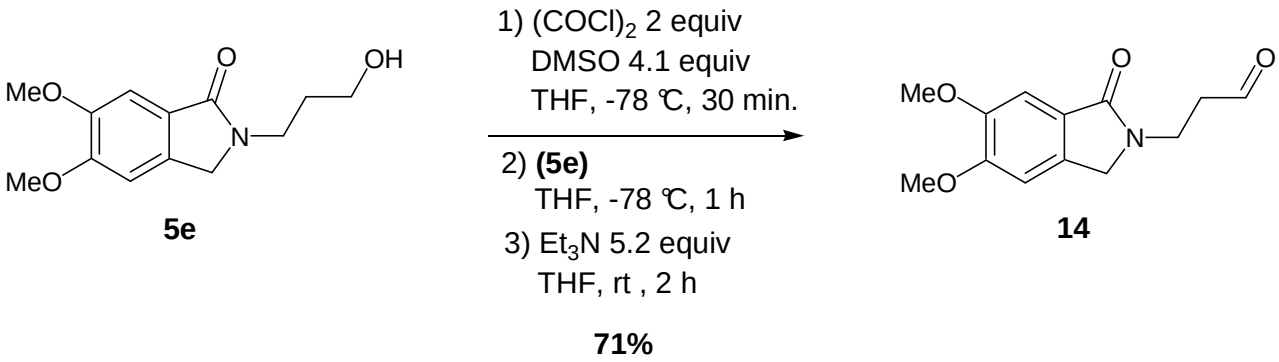
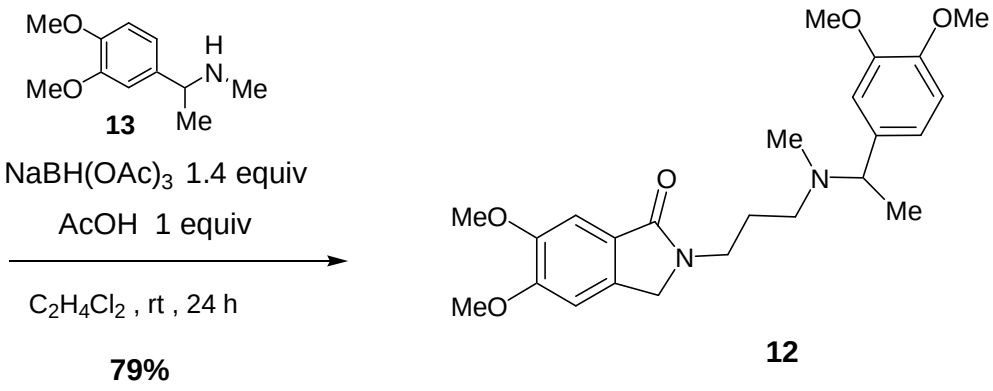
23% yield over six steps

3.2 Synthesis of 2-(3-{[1-(3,4-dimethoxyphenyl)ethyl]methylamino}propyl)-5,6-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one **(12)**

2-(3-{[1-(3,4-Dimethoxyphenyl)ethyl]methylamino}propyl)-5,6-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one (AQ-A 39) (**12**) has been reported to induce cardiovascular actions which might be of benefit in the treatment of ischemic heat disease [11].
This compound was synthesized *via* a reductive amination process involving a suitably substituted secondary benzylamine **13** with an isoindolinone **14** equipped with a carboxyalkyl chain. This compound is the product of the Swern oxidation reaction of the

corresponding hydroxypropyl derivative **5e** which has been prepared by a metalation/anionic cyclization sequence applied to the oxazinone derivative **6e**.





5% yield over nine steps

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