Preparation of Poly and Diversely Substituted N-Alkylated and Free-NH Isoindolin-1-ones

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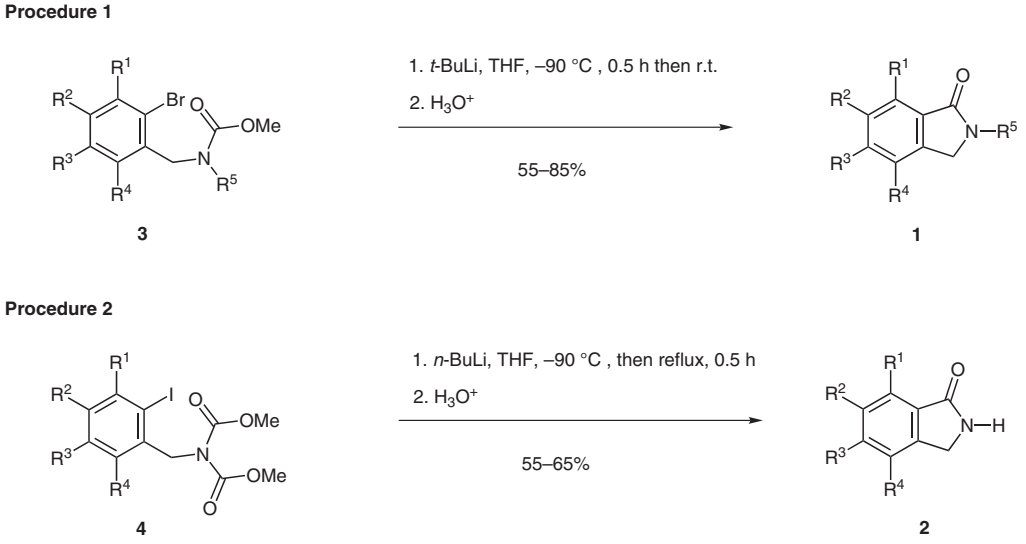
Abstract: A variety of diversely substituted N-alkylated and free-NH isoindolin-1-ones have been efficiently prepared by treatment of suitably substituted di- and monoacylated halobenzylamines, respectively, with a lithiated base.

Key words: lactams, metalations, ring closure



Scheme 1

Isoindolin-1-ones and their derivatives of generic structure **1**, **2** have gained considerable attention due to their diverse and demonstrated physiological and chemotherapeutic activities.[1] The interest in these heterobicyclic models stems also from their importance as key intermediates in organic synthesis namely for the construction of various drugs and biologically active compounds.[2] The isoindolinone moiety is also an integral part of a great variety of naturally occurring compounds, namely alkaloids.[3]

Organic chemists have at their disposal a great number of synthetic methods for the preparation of substituted isoindolinones. The most common synthetic routes are portrayed in Scheme 2, Table 1. All these synthetic strategies are based upon the annulation of an aromatic precursor equipped with appropriate functionalities to ensure the ultimate creation of the lactam unit. It is worth noting that none of these synthetic routes has been secured by exploiting the reactivity and functionalization of the parent phthalimidines. All these synthetic approaches are of procedural simplicity and generally proceed in satisfactory yields. However these methods suffer from several drawbacks and particularly from restrictions in the choice of substituents in their nature, their number and their specific position on the basic aromatic nucleus. Furthermore, the elaboration of free-NH models **2** requires an additional and somewhat erratic deprotection step.[4]

A new synthetic approach to these bicyclic lactams **1**, **2** that is based on the Parham cyclization protocol,[5] i.e., creation of an aryllithiated species by halogen–metal exchange and subsequent trapping by an internal electrophile, has been developed. The procedures summarized in Scheme 1 encompass a unique set of reactions which allow equally well for the assembly of poly, diversely, symmetrically and unsymmetrically substituted N-alkylated and free-NH isoindol-1-one models (Table 2).

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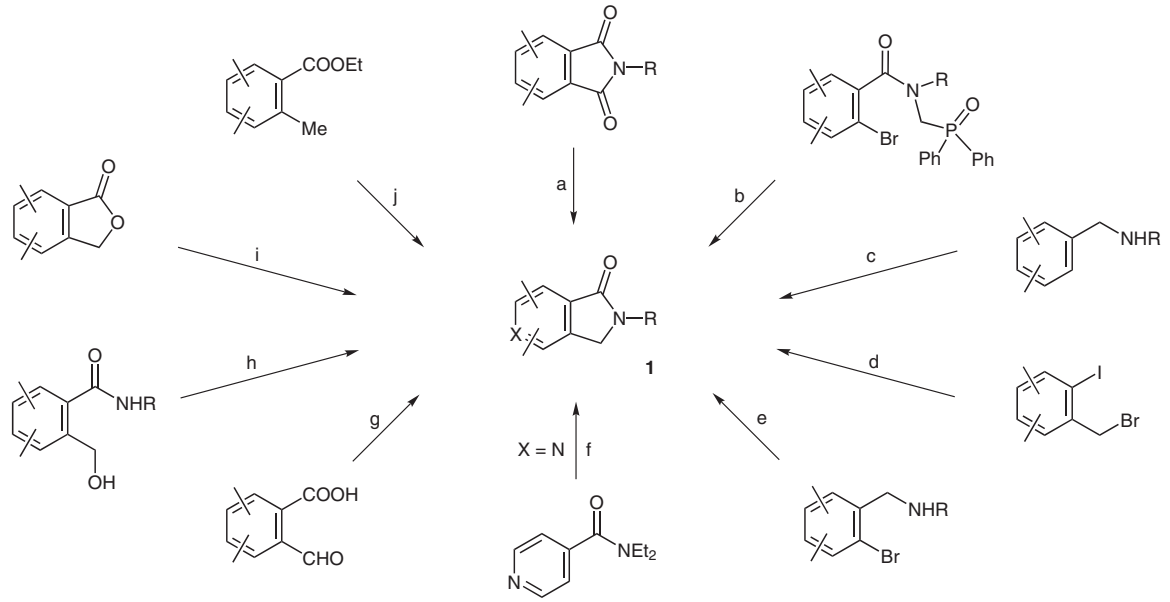


Scheme 2 Synthetic routes to N-alkylated isoindolin-1-ones **1**

Table 1 Reagents and Conditions for the Synthesis of **1**[6–15]

Entry	Reagents and conditions	Ref.
a	Zn, AcOH, reflux	6
b	KHMDS, –78 °C to r.t., then H_2O, OH^-, reflux	7
c	$Pd(OAc)_2/Cu(OAc)_2$, air, CO (1 atm), toluene, reflux	8
d	Pd Cys, CO (1 atm), RNH_2, K_2CO_3, DMF	9
e	PPh_3, *n*-Bu_3N, CO (1 atm)	10
f	LTMP, RCH_2CN, aq NH_4Cl	11
g	RNH_2, AcOH, reflux	12
h	*i*-PrMgCl, DMI, $ClP(O)(NMe_2)_2$	13
i	RNH_2, reflux	14
j	NBS, AIBN, CCl_4, then RNH_2, MeOH	15

In order to ensure the optimal formation of the target annulated compounds **1**, **2**, variations of the metalating agent, temperature profile, and time were screened. The procedures are technically simple and readily provide an array of aromatic bicyclic lactams that can be used for further synthetic planning, e.g., functionalization, but not limited at C-3.[16]

Scope and Limitations

The annulation technique tolerates the presence of fluorinated substituents that survive the halogen–metal interconversion reaction required to secure the lactam unit formation (Table 2, entries 5,6). This process can also be applied to the model compound where the carbamate function is embedded in an oxazolinone ring system, e.g., **3g**, as exemplified by the product benzolactam **1g** equipped with an hydroxyalkyl chain which may serve as a handle for further synthetic development (Table 2, entry 7). Unfortunately, probably due to unfavorable geometry of the parent compound and/or steric congestion of this precursor all attempts to cyclize the bromoaryl piperidine **5** (Figure 1) met with no success.

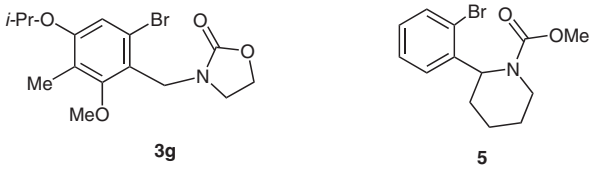


Figure 1 Compounds **3g** and **5**

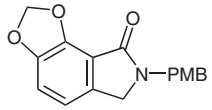
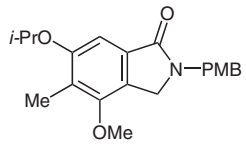
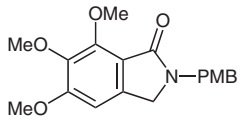
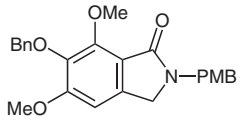
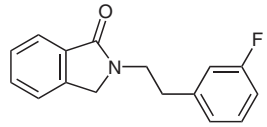
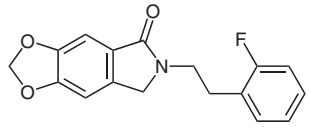
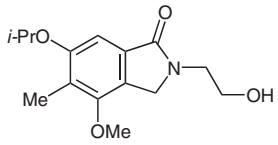
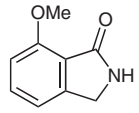
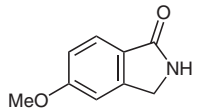
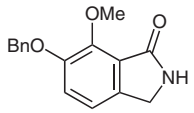
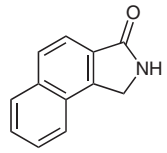
Procedures

Herein we describe two typical procedures for the two substrate classes depicted in Scheme 1 and in Table 2. Some of the products **1**, **2** have not been previously described. Therefore, detailed analytical data for these compounds are provided.

Procedure 1

A solution of *t*-BuLi (1.7 M in pentane, 1.3 mL, 2.2 mmol) was added dropwise at –90 °C under argon to a solution of the carbamate **3** (2 mmol) in THF (30 mL). The solution was stirred at –90 °C for 30 min, and then aq sat. NH_4Cl solution (5 mL) was added. The cooled mixture was extracted with Et_2O (2 × 25 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a solid, which was purified by column chromatography on silica gel using EtOAc–hexanes (50:50) as eluent [acetone–hexanes (80:20) for **1g**] to give the isoindolinone **1** (Table 2).

Table 2 Isoindol-1-ones **1**, **2** Prepared[17–21]

Entry	Product[a]		Yield (%)	Ref.
1		**1a**	63	17
2		**1b**	55	18
3		**1c**	85	–
4		**1d**	82	–
5		**1e**	70	–
6		**1f**	69	19
7		**1g**	69	20
8		**2a**	55	21
9		**2b**	51	21
10		**2c**	64	21
11		**2d**	65	21

[a] PMB: *p*-methoxybenzyl.

6,6,7-Trimethoxy-2-[(4-methoxyphenyl)methyl]-2,3-dihydro-1*H*-isoindol-1-one (1c)
Mp 94–95 °C (hexane–toluene).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 3.84 (s, 6 H), 4.09 (s, 2 H), 4.12 (s, 3 H), 4.62 (s, 2 H), 6.60 (s, 1 H), 6.81 (d, *J* = 8.7 Hz, 2 H), 7.19 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.5, 48.8, 55.3, 56.2, 61.4, 62.6, 101.3, 114.0, 117.4, 129.4, 129.5, 138.7, 141.6, 151.5, 157.0, 159.0, 166.8.

Anal. Calcd for $C_{19}H_{21}NO_5$ (343.4): C, 66.46; H, 6.16; N, 4.08. Found: C, 66.31; H, 6.07; N, 3.92.

6-Benzyloxy-5,7-dimethoxy-2-[(4-methoxyphenyl)methyl]-2,3-dihydro-1*H*-isoindol-1-one (1d)
Oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 3.81 (s, 3 H), 4.10 (s, 5 H), 4.64 (s, 2 H), 5.01 (s, 2 H), 6.60 (s, 1 H), 6.84(d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.25–7.37 (m, 3 H), 7.48–7.50 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6, 48.9, 55.3, 56.2, 62.6, 75.7, 101.4, 114.1, 117.5, 128.0, 128.3, 128.5, 129.4, 129.5, 137.5, 138.9, 140.6, 151.8, 157.3, 159.1, 166.8.

Anal. Calcd for $C_{25}H_{25}NO_5$ (419.5): C, 71.58; H, 6.01; N, 3.34. Found: C, 71.71; H, 6.12; N, 3.53.

2-[2-(3-Fluorophenyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (1e)
Mp 82–84 °C (hexane–toluene).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.96 (t, *J* = 7.3 Hz, 2 H), 3.83 (t, *J* = 7.3 Hz, 2 H), 4.20 (s, 2 H), 6.85–7.00 (m, 3 H), 7.18–7.25 (m, 1 H), 7.35–7.51 (m, 3 H), 7.81 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.6, 43.8, 50.5, 113.5 (d, $J_{C,F}$ = 21 Hz), 115.5 (d, $J_{C,F}$ = 21 Hz), 122.7, 123.6, 124.4 (d, $J_{C,F}$ = 3 Hz), 128.0, 130.1 (d, $J_{C,F}$ = 8 Hz), 131.3, 132.7, 141.1, 141.3 (d, $J_{C,F}$ = 7 Hz), 162.9 (d, $J_{C,F}$ = 244 Hz), 168.5.

Anal. Calcd for $C_{16}H_{14}FNO$ (255.3): C, 75.28; H, 5.53; N, 5.49. Found: C, 75.03; H, 5.65; N, 5.40.

Procedure 2
A solution of *n*-BuLi (1.4 mL, 1.6 M in hexanes, 2.2 mmol) was added dropwise at –90 °C under argon to a solution of the dicarbamate **4** (2 mmol) in anhyd THF (30 mL). The mixture was stirred at –90 °C for an additional 15 min, slowly allowed to warm to r.t. over 1 h, and then refluxed for 30 min. The mixture was cooled to r.t., quenched with aq sat. NH_4Cl solution (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (5 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude oily residue was purified by column chromatography using EtOAc as eluent to afford the annulated compounds **2** (recrystallization from MeCN–Et_2O) (Table 2).

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