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A new simple and convenient synthesis of 3-substituted phthalimidines

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Abstract

An efficient and versatile synthesis of 3-substituted phthalimidines based upon an organometallic reagent addition reduction sequence performed on an appropriate *N*-protected phthalimide is described.

Keywords: Grignard reagents; hydrazides; iminium salts; lactams; phthalimidines.

3-Substituted 2,3-dihydro-1*H*-isoindol-1-ones **1** have attracted much attention from the scientific community, because they represent the core unit of a wide range of naturally occurring substances[1] or bio-active compounds.[1a,c,2] Accordingly, the synthesis of this heterobicyclic system has developed remarkably in recent years, which is also obviously linked to the potential of compounds comprising the 3-substituted phthalimidine unit as synthetic building blocks.[1a,c,3] They are accessible by different chemical processes, which include the rearrangement of six-membered rings,[4] elimination reactions from 3,3-disubstituted compounds,[5] the Parham protocol,[6] or, more recently, a carbocationic pathway.[7]

The most commonly employed synthetic method,[8] however, involves the construction of the lactam unit from an elaborated benzenic precursor in the final step. However, these methods are rather restricted in scope and do not allow the incorporation of a great variety of substituents at the 3-position of the heterocyclic nucleus.

In this paper, we describe a new, concise and efficient synthetic approach to 3-substituted phthalimidines **1** as depicted in the retrosynthetic Scheme 1. The new procedure is based on the sequential addition of an organometallic reagent to an appropriate *N*-protected phthalimide **4**, followed by reduction of the corresponding adduct **3** and subsequent *N*-deprotection of **2** to afford the title compounds. Crucial for the success of our strategy was, therefore, the ability to identify a protecting group (PG), which would be sufficiently robust to survive the projected addition reaction and would also be labile enough

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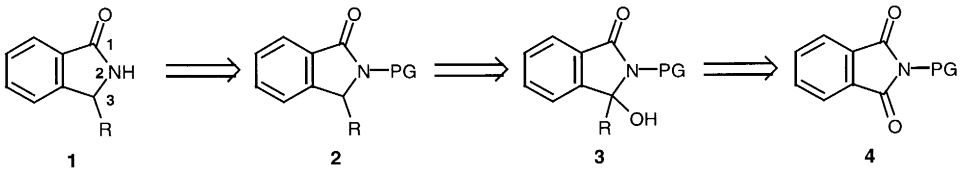
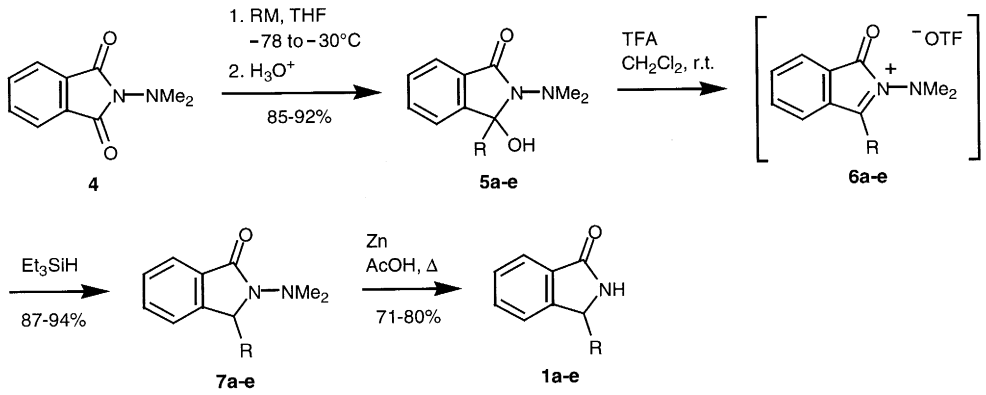
to be removed in the final step. This dual requirement prompted us to incorporate the dimethylamino group (PG=NMe_2) in our model. Besides the fact that additions of organometallic reagents on *N*-amino phthalimides have formed the subject of rather scarce studies,[9] the choice of this group was dictated by the properties of the hydrazine N–N bond, which is well-known to be cleaved under numerous conditions.[10] Furthermore, we anticipated that an electron-withdrawing group connected to the lactamic nitrogen should facilitate the addition step and then should allow the use of indifferently Grignard reagents and more interestingly of lithiated species, which have been rarely employed in this context owing to their higher reactivity. At last, the use of a protecting group should allow a decrease in the amount of the organometallic reagent generally required for nucleophilic additions involving unprotected imides and, consequently, should minimize the formation of by-products.



1 **2** **3** **4**

Scheme 1.

This synthetic route, depicted in Scheme 2, necessitated the preliminary elaboration of the *N*-dimethylamino phthalimide **4**, which was easily obtained[11] by condensation between phthalic anhydride and dimethylhydrazine. As anticipated, we found that the imide **4** reacted readily with a stoichiometric amount of Grignard or organolithium reagents (M=MgX, Li) at low temperature to afford, exclusively, the carbinolamines **5a**–**e** in high yields (Table 1). In order to remove the hydroxy function of these preliminarily formed compounds, *N*,*O*-hemiacetals **5a**–**e** were subsequently treated with an excess of trifluoroacetic acid to give the transient iminium salts **6a**–**e**, which were then smoothly reduced in situ with triethylsilane[12,13] to furnish the *N*-protected bicyclic compounds **7a**–**e**. Finally, removal of the *N*-dimethylamino group in lactams **7a**–**e** was achieved cleanly under reductive acidic conditions by heating with an excess of zinc in refluxing acetic acid[14] to deliver the targeted 3-substituted phthalimidines **1a**–**e** in good yields.



4 **5a-e** **6a-e** **7a-e** **1a-e**

Scheme 2.

By means of a new synthetic approach, involving the addition of an organometallic reagent over a protected phthalimide as the key step, and followed by the reduction of the intermediate carbinolamines and a deprotection step, we have disclosed a concise and efficient synthesis of 3-substituted 1-isoindolinones. Owing to the efficiency and simplicity of this methodology, this process deserves attention and further

Table 1
Generation of compounds **5**, **7** and **1**

			5		**7**		**1**	
Entry		RM	Yield (%)	mp (°C)	Yield (%)	Mp (°C)	Yield (%)	mp (°C)
1	**a**	MeMgI	92	168-169	94	oil	76	118-119[8a]
2	**a**	MeLi	87					
3	**b**	*n*-BuLi	87	oil	89	oil	71	88-89[5b]
4	**c**	*t*-BuLi	85	133-134	90	100-101	78	185-186[15]
5	**d**	*n*-HexLi	86	oil[16]	87	oil[17]	73	84-85[18]
6	**e**	PhMgBr	90	173-174	94	151-152	80	218-219[19]
7	**e**	PhLi	85					

work aimed at performing these reactions with asymmetric induction by means of chiral hydrazines is currently under investigation in our laboratory.

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16. Selected data for compound **5d**: oil; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 0.88–1.40 (m, 11H), 2.14–2.24 (m, 2H), 2.99 (s, 6H, NMe_2), 4.94 (br. s, 1H, OH), 7.43–7.66 (m, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: *C* 166.0 (CO), 144.6, 130.4, 90.6, *CH* 131.8, 128.7, 122.5, 121.7, CH_2 35.6, 31.1, 28.8, 23.7, 22.1, CH_3 44.7, 13.6. MS, *m/z* (%): 276 (M^+, 11), 59 (100). IR (KBr) 1683 (CO), 3363 (OH).
17. Selected data for compound **7d**: oil; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 0.83 (t, *J*=6.9 Hz, 3H), 0.91–1.10 (m, 1H), 1.14–1.33 (m, 7H), 2.97 (s, 6H, NMe_2), 4.43 (dd, *J*=6.0, 4.0 Hz, 1H, NCHAr), 7.31–7.44 (m, 2H, H_{arom}), 7.49 (dt, *J*=7.4, 1.4 Hz, 1H, H_{arom}), 7.75 (d, *J*=7.4 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: *C* 167.5 (CO), 144.1, 132.4, *CH* 131.4, 127.8, 123.1, 122.3, 61.0, CH_2 31.6, 30.8, 29.4, 23.5, 22.5, CH_3 44.1, 14.0. MS, *m/z* (%): 260 (M^+, 31), 218 (98), 146 (100), 132 (54). IR (KBr) 1699 (CO).
18. Selected data for compound **1d**: mp 84–85°C; ^{1}H NMR ($CDCl_3$, TMS) δ ppm: 0.83 (t, *J*=6.9 Hz, 3H, Me), 1.18–1.51 (m, 7H), 1.57–1.68 (m, 1H), 1.87–1.99 (m, 1H), 4.60 (dd, *J*=7.4, 4.7 Hz, 1H, NCHAr), 7.38–7.46 (m, 2H, H_{arom}), 7.52 (dt, *J*=7.4, 1.1 Hz, 1H, H_{arom}), 7.82 (d, *J*=7.4 Hz, 1H, H_{arom}), 8.22 (br. s, 1H, NH); ^{13}C NMR ($CDCl_3$, TMS) δ ppm: *C* 171.3 (CO), 147.8, 132.0, *CH* 131.5, 127.8, 123.6, 122.3, 57.2, CH_2 34.6, 31.6, 29.2, 25.5, 22.6, CH_3 14.1. MS, *m/z* (%): 217 (M^+, 16), 132 (100). IR (KBr) 1686 (CO), 3192 (NH).
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