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LDA-Induced Metalation of Isoindolinones. An Efficient Route to 3-Substituted Isoindoline Derivatives

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Abstract: 3-Substituted isoindolines have been efficiently prepared by sequential lithiation and reduction of isoindolinones.

The literature contains a number of efficient procedures for the creation of carbanionic species but the generation of benzylic anions, which are of great synthetic utility for functionalization or chain extension of benzylic sites, still remains a challenging task. Benzylic metalation can be achieved with the "superbase" combination of alkyllithium and potassium alkoxyde reagents[1] or by lithium-tellurium exchange of tellurides[2] but these harsh conditions are rarely compatible with the presence of other sensitive functionalities. To obviate such problems the benzylic position can be flanked by a heteroatom-containing substrate (HS) which facilitates generation of the α-metalated species, thus allowing the use of weaker base such as LDA or LTMP.[3] Recently these heteroatom-promoted lithiation reactions have been extensively reviewed by Clark and Jahangir.[4] Examination of the literature shows that the heteroatomic entity may be connected either to the carbon atom adjacent to the benzylic position or directly embedded in a heterocyclic framework (Fig. 1) as in the case of phthalides[5] and thiophthalides.[6] Paradoxically, despite the fact that the *N,N*-dialkylcarboxamide group ranks high in the hierarchy of the heteroatomic entities capable of promoting lateral metalation of benzylic systems,[4] to our knowledge, the lithiation reactions of isoindolinones have not yet been reported.

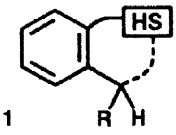

Fig. 1

We report now that, as expected, 2-alkyl-2,3-dihydroisoindol-1-ones **1,2** are easily and regioselectively deprotonated at the 3-position of the heterocyclic nucleus with LDA, thus providing ready access to 3-substituted and/or functionalized isoindolinones and consequently to the corresponding isoindolines.

Thus, lithiation of the isoindolinones **1,2**[7] occurred smoothly and rapidly with 1.1 equiv. of LDA in THF at -78°C to give the lithio species **3**. It is noteworthy that the *N,N*-dialkylcarboxamido function is a powerful activator for the *ortho*-metalation[8] but in the competitive process involving *ortho versus* adjacent benzylic lithiation, adjacent α-lithiation is favoured over *ortho*-lithiation. This can be due, in part, to an insufficient kinetic basicity of lithium dialkylamides for the *ortho*-directed metalation process. Quenching anion **3** with a diverse array of electrophiles resulted in the formation of the corresponding 3-substituted isoindolinones **4a-g** and **5a,b,e,h** in good yields.[9] Previously such compounds have been obtained mostly by addition of *ortho*-substituted aryllithium reagents to imines,[10] but this method only allows the introduction of aryl and alkyl units onto the five-membered heterocyclic moiety. Reduction of the substituted isoindolinones proceeded

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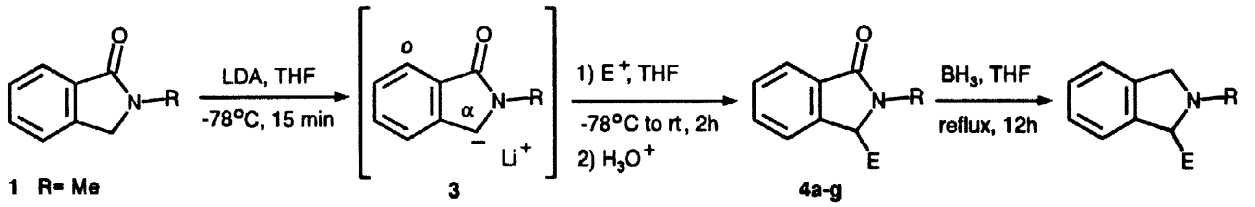

1 R= Me
2 R= 4-MeOC$_6$H$_4$

3

4a-g
5a,b,e,g

6a,b,e

	R	E (Reagent)	mp (°C)	Yield (%)
4a	Me	Me (Me_2SO_4)	oil	69
4b	Me	Bn (BnBr)	-	62
4c	Me	CH_2=CH-CH_2 (CH_2=CH-CH_2Br)	-	86
4d	Me	MeS (Me_2S_2)	-	46
4e	Me	PhCHOH (PhCHO)	207-208	97
4f	Me	PhCO (PhCON(OMe)Me)	136-137	39
4g	Me	PhCH-NHMe (PhCH=NMe, BF_3.OEt_2)	113-114	52
5a	4-MeOC$_6$H$_4$	Me (Me_2SO_4)	oil	69
5b	4-MeOC$_6$H$_4$	Bn (BnBr)	-	53
5e	4-MeOC$_6$H$_4$	PhCHOH (PhCHO)	157-158	98
5g	4-MeOC$_6$H$_4$	COOH (CO_2)	124-125	88

uneventfully, as shown by the conversion of **5a,b,e** to the corresponding isoindolines **6a,b,e** in fairly good yields[11] by treatment with BH_3 in THF. The presence of the 4-methoxybenzyl amino-protecting group in these substrates and the possibility of incorporating other functionalities in the heterocyclic nucleus endows the procedure with considerable synthetic potential. Further work in this direction is now in progress.

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9. Compound **4e** (two diastereomers, 85:15). Typical data for the major isomer: ^{1}H NMR (DMSO-*d6*; 300 MHz) δ 3.14 (3H, s), 4.87 (1H, d, J = 3.0Hz), 5.32 (1H, dd, J = 3.0, 4.5 Hz), 5.71 (1H, J = 4.5 Hz), 6.67-6.72 (1H, m), 7.22-7.45 (7H, m), 7.50-7.55 (1H, m); ^{13}C NMR (DMSO-*d6*, 75 MHz) δ: 33.5, 72.0, 76.0, 127.4, 128.6, 131.5, 132.3, 132.9, 133.0, 135.5, 138.3, 146.0, 147.5, 173.0.
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11. **6a** (82%), **6b** (75%), **6e** (78%). Typical data for compound **6e**: ^{1}H NMR ($CDCl_3$; 300 MHz) δ 3.43 (1H, d, J = 13.0 Hz), 3.60 (1H, d, J = 13.0 Hz), 3.80 (1H, d, J = 14.3 Hz), 3.83 (3H, s), 4.28 (1H, d, J = 14.3 Hz), 4.38 (1H, d, J = 4.1 Hz), 4.79 (1H, d, J = 4.1 Hz), 6.87 (2H, d, J = 6.8 Hz), 7.10-7.46 (11H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.3, 58.3, 60.0, 73.9, 75.9, 113.9, 122.5, 123.1, 126.0, 126.9, 127.0, 127.3, 127.7, 128.4, 128.5, 130.0, 158.8.