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A General Method for the Synthesis of Isatins: Preparation of Regiospecifically Functionalized Isatins from Anilines

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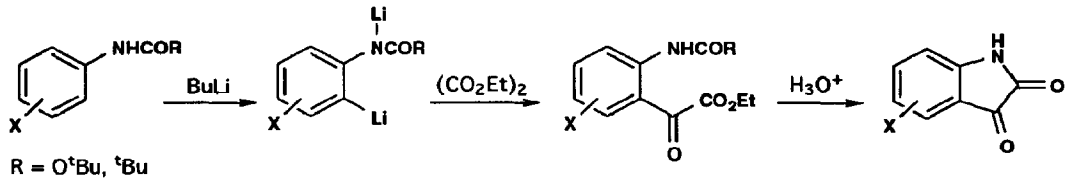
Abstract: A new method has been developed for regiospecific conversion of substituted anilines to isatins. The method utilizes the reaction of an *ortho*-lithiated, protected aniline derivative with diethyl oxalate to furnish an α-ketoester. Hydrolytic deprotection of the amino moiety is accompanied by cyclization to provide the isatin.

Isatins have been used as valuable synthetic intermediates in both the pharmaceutical and dye industries for many decades.[1] The most commonly used method for the preparation of isatins is the Sandmeyer procedure.[2] This protocol involves the formation of an isonitrosoacetanilide from an aniline followed by acid catalyzed cyclization to the isatin. Another frequently used method by Stolle[3] involves initial treatment of an aniline with oxalyl chloride followed by Friedel-Crafts-type intramolecular acylation in the presence of a strong Lewis acid. Since both methods require electrophilic attack on the aromatic ring, the presence of strongly electron-withdrawing substituents tends to inhibit the reaction. The Gassman[4] synthesis of isatins depends on the conversion of anilines into 3-(methylthio)oxindoles followed by oxidative removal of methylthio group via chlorination and subsequent hydrolysis. One advantage of the Gassman synthesis is that the method is compatible with the presence of either strongly electron-withdrawing or electron-donating groups. However, these three commonly used methods suffer from lack of regioselectivity and *meta*-substituted anilines generally give rise to a mixture of 4- and 6-substituted isatins. We now wish to report a new general method for the synthesis of isatins starting from anilines. This method is insensitive to the electronic nature of substituents bound to the aromatic ring and is characterized by predictable regiochemical control.

It is well established that when the amino group of an aniline is suitably protected it can direct metalation to the *ortho* position.[5-9] N-Pivaloylanilines[5] and N-(*tert*-butoxycarbonyl)anilines[6-8] have been used widely to prepare *ortho*-substituted aniline derivatives via the corresponding dianion species. Our strategy hinged upon the reaction of these dianions with diethyl oxalate to introduce an α-keto-ester moiety *ortho* to the protected amino group of the aniline. Removal of the amino protecting group followed by cyclization should then provide the isatin.

Although a variety of α-keto esters have been prepared by the reaction of Grignard and organolithium reagents with diethyl oxalate,[10-14] the reaction of dianions of protected anilines has not been reported. We have found that the reaction of these dianion species with 1.2 equivalents of diethyl oxalate at -78 °C generates the desired α-keto esters in excellent yield, as depicted in the Scheme. Hydrolytic removal of the *tert*-butoxycarbonyl or pivaloyl protecting group was accompanied by spontaneous cyclization to afford the isatin.

Scheme

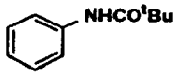
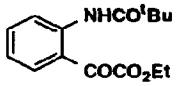
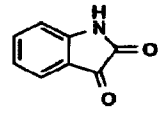
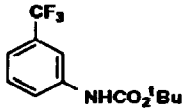
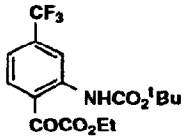
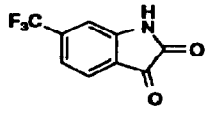
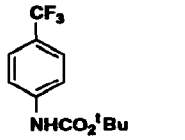
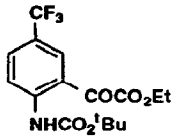
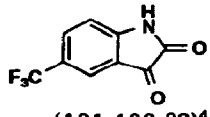
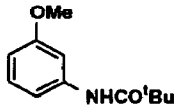
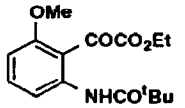
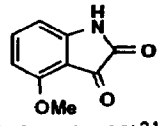
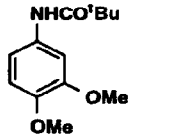
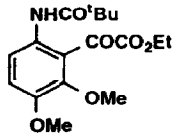
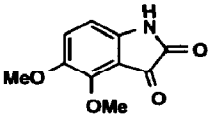
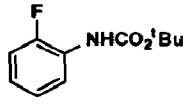
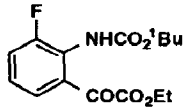


R = O^{t}Bu, ^{t}Bu

The dianions of N-pivaloylanilines and N-(*tert*-butoxycarbonyl)anilines were generated using 2.2 to 2.4 fold excess of a variety of butyllithium reagents in THF,[5a,15-18] as summarized in the Table. In a typical procedure, neat dry diethyl oxalate (1.2 equivalents) was added rapidly to a solution of the dianion stirred at -78 °C under nitrogen. After being strirred for 30-45 minutes, the reaction mixture was quenched with IN HCl and diluted with diethyl ether. The crude keto-ester was purified either by recrystallization or flash chromatography. Deprotection of the *tert*-butoxycarbonyl[19] or pivaloyl moieties was performed using 3N HCl/THF and 12N HCl/DME, respectively, at reflux, as indicated in the Table. Upon evaporation of the volatile solvents, the isatins precipitated from the aqueous residue and were isolated by filtration.

From the results summarized in the Table, it is apparent that the yields for the individual steps of this procedure are generally excellent. Although the intermediate α-ketoesters were purified for purposes of characterization, this step is not necessary and the crude product can be deprotected directly to afford the isatins in excellent overall yield. The relatively poor yield associated with the preparation of the parent α-ketoester (entry 1) most likely reflects the metalation step, known to be problematic.[5a] The pattern of substitution of the isatins produced by this method is dependent upon the regiospecificity of the directed metalation, which has been established for many substituted aniline derivatives. Particularly noteworthy is the fact that the isomeric CF_3-substituted isatin derivatives (entries 2 and 3) are now readily accessible by a common procedure, which contrasts with the individual syntheses previously reported for these compounds.[20,21] Moreover, this procedure provides a rapid and efficient method for the preparation of 7-fluoroisatin for which the Sandmeyer protocol has been reported to be ineffective.[23b]

Table: Preparation of ketoester intermediates and isatins from protected anilines.

Entry	protected aniline	metalation conditions	keto-ester	% yield	hydrolysis conditions	isatin (mp)[ref]	% yield
1		*n*-BuLi, THF[5a] 0 °C, 6-7 h		59	12N HCl-DME reflux	 (190-192 °C)	79
2		*s*-BuLi, THF[15] -40 °C, 2 h		85	3N HCl-THF reflux	 (196-198 °C)[20]	87
3		*s*-BuLi, THF[16] -40 °C, 2 h		67	3N HCl-THF reflux	 (191-193 °C)[4]	89
4		*n*-BuLi, THF[5a] 0 °C, 3 h		80	12N HCl-DME reflux	 (197-198 °C)[21]	88
5		*n*-BuLi, THF[17] 0 °C, 3 h		83	12N HCl-DME reflux	 (194-196 °C)[22]	83
6		*t*-BuLi,THF[18] -40 °C, 2 h		81	3N HCl-THF reflux	 (190-192 °C)[23a]	87

All new compounds exhibited spectroscopic and combustion data in accord with the designated structure.[24]

In summary, we have developed a simple and efficient procedure for preparation of regiospecifically functionalized isatins from anilines that offers considerable synthetic advantage over previously described methods. This protocol, which complements existing procedures, is applicable to a variety of substituted aniline derivatives and will be useful for the preparation of highly functionalized isatins.

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24. Spectroscopic data for keto-ester intermediate of entry 1: IR (film) cm^{-1} 3318, 2968, 1740, 1698, 1652, 1530, 1196, 752; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (9 H, s), 1.40 (3 H, t), 4.44 (2 H, q), 7.10 (1 H, t), 7.60 (1 H, d), 7.65 (1 H, t), 8.83 (1 H, d), 11.36 (1 H, brd s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.09, 27.51, 40.51, 62.65, 117.20, 120.67, 122.32, 133.62, 137.18, 143.24, 163.68, 178.45, 190.70; MS m/e 278 (MH^+), 204.

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