Pergamon

Tetrahedron Letters 39 (1998) 7679–7682

TETRAHEDRON LETTERS

An Improved Procedure for the Regiospecific Synthesis of Electron Deficient 4- and 6-Substituted Isatins.

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Received 22 July 1998; revised 10 August 1998; accepted 11 August 1998

Abstract The regiospecific synthesis of 4- and 6-substituted isatins **5a-g** in four steps from halonitrobenzenes **1a-g** has been investigated for a variety of substrates (Scheme 1). The procedure makes use of readily available, easily handled materials and in most cases purification of neither intermediates nor final products is required. Yields of isatins are between 26 and 75% (Table 1). Improved yields of known isatins are reported as well as the syntheses of previously unreported isatins. This method, taken together with known procedures, provides for the synthesis of the full complement of isatin regioisomers.

Keywords: Annulation; Nitrogen heterocycles; Nitro compounds; Regiospecificity

Introduction

Isatins have found broad use in the pharmaceutical industry.[1-3] In the course of our work we became interested in making a variety of isatins substituted at the 4- and 6-positions, primarily with benzoyl groups and halogens. The lack of recent, suitable methodology capable of providing regiospecifically 4- or 6-haloisatins was not encouraging. The most commonly utilized methods for synthesizing isatins reveal a common element, that of annulation of an aniline derivative.[1, 3-7] Annulation of *meta*-substituted aniline derivatives, which are required for 4- or 6-substituted isatins, is problematic due to the lack of regiospecificity. Moreover, isatins are insoluble in all but the most polar solvents (*e.g.* DMSO, hot DMF) which makes purification of mixtures impractical. Methods of generating isatins from 5,6-fused ring systems were deemed not useful for our work due to the fact that the desired substitution pattern would have to have been present in the starting materials, which in turn are usually made through the annulation of aniline derivatives.[8, 9] However, we were intrigued by a few examples where an indole was transformed to a 3,3-dihalo-2-oxindole, then to an isatin *via* hydrolysis[10]. This led us to believe that if one could procure 2-oxindoles with regiochemical control, a similar path (bishalogenation, hydrolysis) would make the selective synthesis of 4- and 6-substituted isatins possible. Herein we describe an efficient method of producing such compounds.

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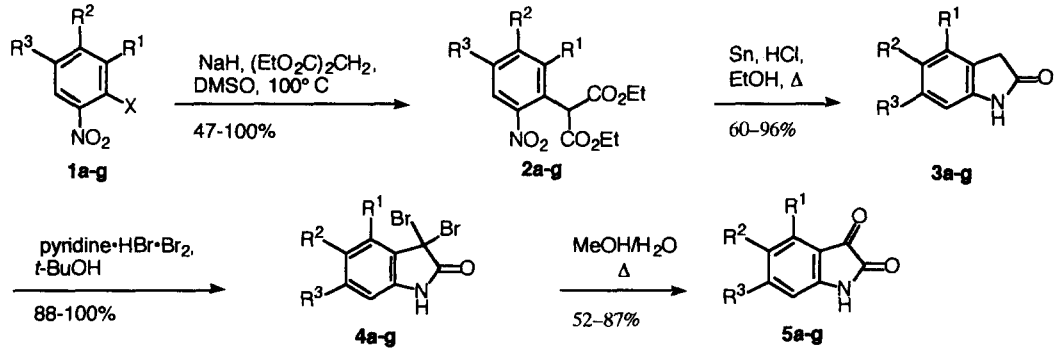
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01719-5

Results

We prepared several 2-oxindoles by the method of Walsh and co-workers (Scheme 1).[11] Nucleophilic attack of a malonate anion on appropriately substituted *ortho*-halonitrobenzenes[12] **1a-g** proceeded in a regiospecific manner. Frequently, the malonate adducts were contaminated with diethyl malonate but this did not affect the subsequent reduction step. The nitromalonates **2a-g** were then reduced with concomitant amide formation and decarboxylation to afford the 4- or 6-substituted 2-oxindoles **3a-g** by treatment with Sn/HCl. The 2-oxindoles were then treated with pyridinium bromide perbromide to furnish clean 3,3-dibromo-2-oxindoles **4a-g**, which were used immediately in the last step. Hydrolysis of these intermediates in aqueous methanol afforded clean isatins **5a-g**. The results, summarized in Table 1, show that the overall yields of isatins were 26-75%. In the case of 4-chloroisatin **5a** silica gel chromatography was required after the first step only to dispose of unreacted starting material.



a: R^1=Cl; R^2,R^3=H; X=Cl
b: R^1, R^2=H; R^3=Cl; X=Cl
c: R^1=H; R^2,R^3=Cl; X=F
d: R^1, R^2=H; R^3=benzoyl; X=Cl
e: R^1, R^2=H; R^3=4-methylbenzoyl; X=Cl
f: R^1, R^2=H; R^3=4-chlorobenzoyl; X=Cl
g: R^1, R^2=H; R^3=4-methoxybenzoyl; X=Cl

Scheme 1

General Procedure for the Preparation of 2-Oxindoles 3a-g

The procedure of Walsh[11] was employed to transform malonate adducts **2a-g** to oxindoles. In the cases of the chlorooxindoles **3a-c** the decanted solution was stirred vigorously and neutralized cautiously with saturated $NaHCO_3$ solution, until foaming had ceased and the mixture had an approximate pH of 8. The tin salts were collected on a Büchner funnel, washed with H_2O and suctioned dry. The dry filter cake was pulverized with a mortar and pestle, transferred to an Erlenmeyer flask and stirred with boiling EtOAc, then filtered while hot and washed with hot EtOAc. Removal of the solvent with a rotary evaporator furnished the product. Both methods of isolation provided products which did not require purification.[13] This procedure was used to prepare 2-oxindoles on scales from 1 to 140 mmol.

General Procedure for the Preparation of 3,3-Dibromo-2-oxindoles 4a-g

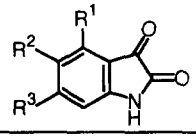
Oxindole **3a-g** (0.53 mmol) was dissolved in 5 mL of *t*-BuOH and H_2O was added (23 μL, 1.27 mmol). Pyridinium bromide perbromide (679 mg, 2.12 mmol) was added in one portion and the mixture was stirred for 16 h. The solution was diluted with 5 mL of H_2O, stirred until the solid dissolved and extracted with EtOAc (3 x 2 mL). The organic extracts were washed with H_2O (4 x 3 mL), dried over Na_2SO_4, filtered and concentrated on a rotary evaporator (CAUTION: condensate contains Br_2) and then on a vacuum line to remove all Br_2 to afford a crude product which was used immediately in the next step.[13] This procedure was used to prepare 3,3-dibromo-2-oxindoles on scales from 0.53 to 19 mmol.

General Procedure for the Preparation of Isatins ***5a-g***

3,3-dibromo-2-oxindole **4a-g** (8.53 mmol) was suspended in 24 mL of MeOH-H_2O (4:1 v/v) and heated at reflux for 50 h. The reaction mixture was then cooled in ice, the resulting precipitate was filtered, washed once with ice-cold MeOH, then with H_2O until the washings were neutral, affording the product. Any insoluble material in the reaction flask or solid in the filtrate was discarded. This procedure was used to prepare isatins on scales from 0.50 to 18 mmol.

Table 1

Preparation of nitromalonate, oxindole and dibromooxindole intermediates and isatin products



R^1	R^2	R^3	displacement product/yield	reduction product/yield	bromination product/yield	hydrolysis product/yield	overall yield
Cl	H	H	**2a** 47%[a]	**3a** 78%[b]	**4a** 88%	**5a** 80%	26%
H	H	Cl	**2b** 84%	**3b** 79%[b]	**4b** 99%	**5b** 57%	37%
H	Cl	Cl	**2c** 97%	**3c** 95%[b]	**4c** 100%	**5c** 70%	65%
H	H	benzoyl	**2d** 60%	**3d** 96%	**4d** 100%	**5d** 75%	43%
H	H	4-methylbenzoyl	**2e** 98%	**3e** 60%	**4e** 89%	**5e** 57	30%
H	H	4-chlorobenzoyl	**2f** 99%	**3f** 65%	**4f** 88%	**5f** 52%	29%
H	H	4-methoxybenzoyl	**2g** 100%	**3g** 88%	**4g** 98%	**5g** 87%	75%

[a] The crude product was contaminated with starting material and required purification. [b] Product isolation required cleavage of the tin intermediate with $NaHCO_3$ solution. See the general procedure in the text.

Discussion

A comparison of the present work with the published syntheses of the 4-, 6-[14] and 5,6-dichloroisatins[15] (**5a-c**) using the Sandmeyer method illustrates the utility of our route. The latter process gives overall yields from anilines of 45, 29 and 17%, respectively. The 4- and 6-chloroisatin isomers are purified by tedious fractional precipitation with acid, which requires much trial and error. 5,6-Dichloroisatin is prepared by treating 6-chloroisatin (made by the Sandmeyer method) with chlorine gas, followed by recrystallization to remove unreacted starting material. By comparison, our method furnishes the same compounds in overall yields from the halonitrobenzenes of 25, 37 and 65%, respectively. Most importantly, only the desired compound is produced, unlike the Sandmeyer procedure, in which half of the reaction product is undesirable. A lower yield of **5a** was anticipated due to steric considerations. Nevertheless, it may be preferable to the disposal of unwanted isomer.

Our method also provides a route to 6-benzoyl isatins. When Walsh and co-workers employed the Gassman procedure in their work in benzoyl-substituted oxindoles and isatins, they were only able to obtain the 4-isomers. They attributed this to the moderately strong electron-withdrawing nature of the carbonyl group.[11]

We wish to point out that this method is limited to the use of moderately to strongly electron-withdrawing groups. Attempts to make 4-bromo- and 6-iodoisatin (precluded by Sandmeyer's[3] and Hewawasam's[7] methods)

failed due to bromination of the oxindoles at the 5-position of the aromatic ring.[16] Attempts to make 6-methyl- and both 5- and 6-methoxyisatin (precluded by Hewawasam's method) failed for the same reason.

Conclusion

We report an improved method for the regiospecific synthesis of 4- and 6-substituted isatins. The method is the most efficient one known to us, requiring four steps from the halonitrobenzene starting material. Purification generally is not necessary and overall yields of isatins are between 26 and 75%. It allows the preparation of the previously unreported 6-benzoylisatins. Taken together with known methods, it is now possible to synthesize isatins bearing substituents in the 4-, 5-, 6- and 7-positions in a regioselective manner.

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