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Synthesis of substituted isatins

Larry L. Klein *, Michael D. Tufano

Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, 833 S. Wood Street, Chicago, IL 60612, United States

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ABSTRACT

Isatins are valuable intermediates for heterocyclic chemistry. Most of the common methods for their production are less than adequate when the number and lipophilicity of substituents on the targeted isatin are increased. Our group desired such molecules and identified an alternative method for their production.

Isatins (1*H*-indole-2,3-diones, **1**) are valuable intermediates in the field of heterocyclic and pharmaceutical chemistry.[1] Several of these derivatives show activities of biological interest[2] but most serve as templates in the construction of pharmaceutically active agents. Recently, we required multiply substituted isatins as intermediates and found the standard methods for their preparation to be less than optimal on a gram scale.[3]

The most common procedure for the synthesis of isatins is the Sandmeyer process[4] which utilizes a mixture of chloral hydrate, an aniline (or its hydrochloride salt), hydroxylamine, and hydrochloric acid in a heated sodium sulfate-saturated aqueous media (Fig. 1). The molecular mechanism for this process is believed to proceed through an initial glyoxamide **4** which reacts, in turn, with hydroxylamine to form oximinoacetanilide, **5**.[5a,b] Heating compound **5** to 90 °C in sulfuric acid affects the ring cyclization to produce isatin, **1**.

Although this process has worked for simple analogs (Fig. 1, 2a), as the substitution of the precursor anilines increases both in number and lipophilicity, the facility of this classical reaction to form the oximinoacetanilide intermediate **5** suffers. For example, when 4-*n*-hexylaniline (**2b**) was used as starting material, <5% yield of intermediate **5b** could be isolated. Attempts to modify this process through the use of co-solvents such as ethanol[6a] or microwave heating[6b] have helped obtain some products not otherwise available, albeit in moderate yields. The fact that the key reagent, chloral hydrate, is a regulated substance also impacts the potential to perform large scale production of the isatins.

An alternative method for production of intermediate **5** or its equivalent was envisioned involving a coupling reaction of an alkyloximinoacetic acid **6** (Fig. 2) and an aniline under standard amide-forming conditions; however, though hydroxyiminoacetic acid (**6a**) is known,[7] reaction of this compound with anilines failed to provide product **5**. Crystalline benzyloximinoacetic acid (**6b**) is available in multi-gram quantities via an extractive work-up following combination of *O*-benzylhydroxylamine and glyoxylic acid hydrate.[8] Coupling of **6b** to a variety of substituted anilines led to good yields of the benzyloximinoacetanilides, **7** as shown in Table 1. The corresponding benzyloximinoacetyl chloride (**8**) is also available via treatment of **6b** with oxalyl chloride and serves equally well to produce substituted anilines **7** in the presence of bases such as triethylamine or diisopropylethylamine in common organic solvents (e.g., dichloromethane, tetrahydrofuran).

It has been suggested that the ring cyclization step in the Sandmeyer process involves a dehydration of the oxime to form α-acylnitrile (Fig. 1). In the case of the benzyl analog, rather than loss of water, the loss of benzyl alcohol would have to take place to form this same reactive intermediate. When **7a** was treated in this manner, the isatin product was formed in a similar yield as for the unsubstituted oximinoacetanilide, **5**. Since no chemical trace of the benzyl residue was apparent from this modified reaction, it is presumed that any such alkyl moiety can be used in this approach. This reaction sequence was carried out at a 10 g scale without change in the yield of isatin **9** produced (Table 2, entry 1).

When oximinoacetanilide analogs of high lipophilicity (e.g., **7f–h**) were heated in sulfuric acid as per the classical Sandmeyer route, cyclization was frequently incomplete due to the poor solubility under these conditions. Use of methanesulfonic acid[9] as the media with these three oximinoacetanilides proved to be helpful in circumventing the problems and served to provide the corresponding isatin products even when little or no product was available from the sulfuric acid method (Table 2). In general, yields of

* Corresponding author. Tel.: +1 312 413 9440; fax: +1 312 355 5539.
E-mail address: llk@uic.edu (L.L. Klein).

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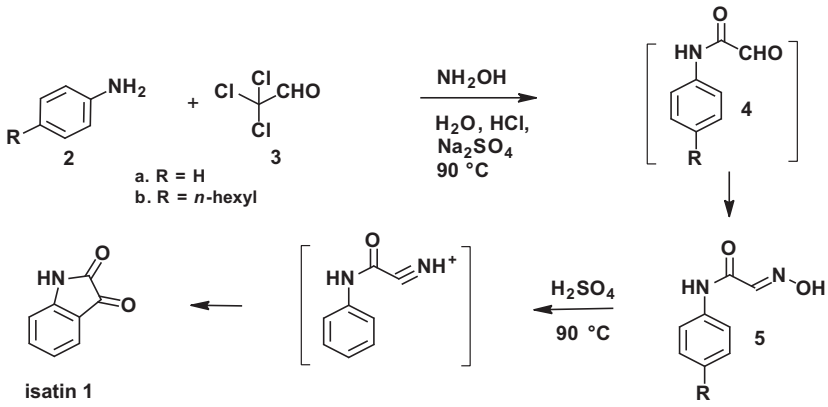


Figure 1. Sandmeyer isatin process.

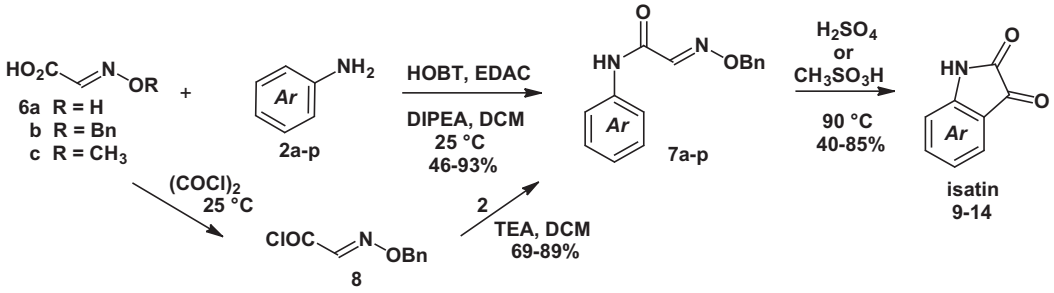
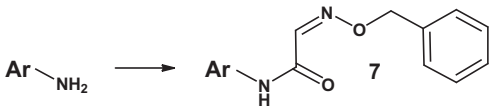
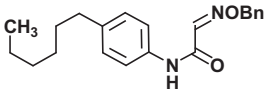
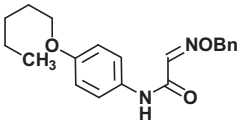
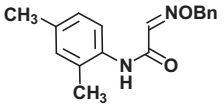
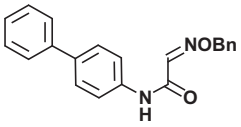
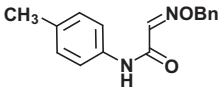
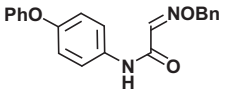
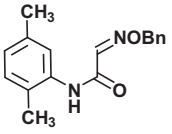
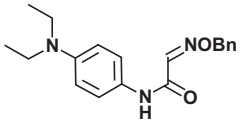
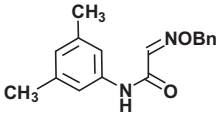
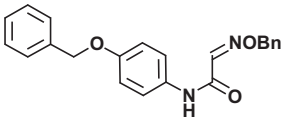
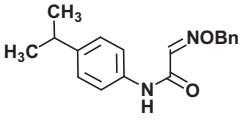
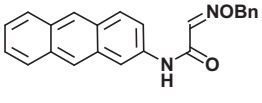


Figure 2. Synthesis of alkyloximinoacetanilides **7**.

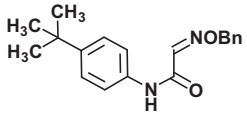
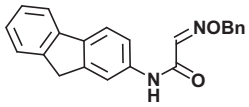
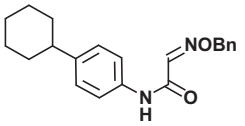
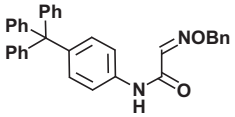
Table 1
Preparation of benzyloximinoacetanilides



Entry	Product	Compd #	Method[a]	Yield (%)	Entry	Product	Compd #	Method[a]	Yield (%)
1		**7a**	A	85	9		**7i**	B	80
2		**7b**	B	75	10		**7j**	A	46
3		**7c**	B	69	11		**7k**	A	60
4		**7d**	A	79	12		**7l**	B	79
5		**7e**	B	87	13		**7m**	B	89
6		**7f**	A	93	14		**7n**	B	61

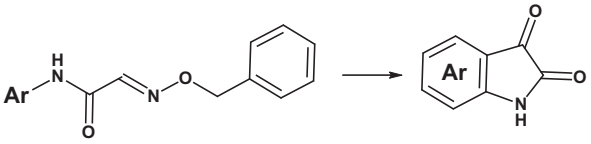
(*continued on next page*)

Table 1 (*continued*)

Entry	Product	Compd #	Method[a]	Yield (%)	Entry	Product	Compd #	Method[a]	Yield (%)
7		**7g**	B	88	15		**7o**	B	71
8		**7h**	B	89	16		**7p**	B	87

[a] Method A: $ArNH_2$, 1 equiv $HO_2CCH{=}NOBn$, 1.5 equiv EDAC, 1.5 equiv HOBt, 3 equiv DIPEA, THF, rt; or Method B: $ArNH_2$, 1.05 equiv $ClCOCH{=}NOBn$, 1.15 equiv TEA, DCM, rt.

Table 2
Preparation of isatins



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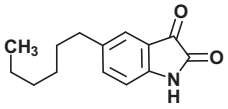
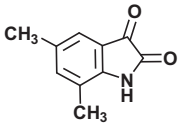
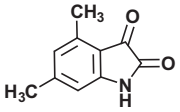
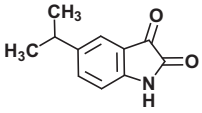
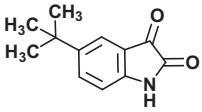
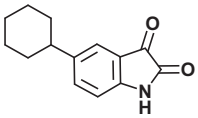
1		**9**	H_2SO_4	85
2		**10**	H_2SO_4	60
3		**11**	H_2SO_4	46
4		**12**	CH_3SO_3H	40
5		**13**	CH_3SO_3H	64
6		**14**	CH_3SO_3H	60

[a] Method A: H_2SO_4 at 50 °C, heat to 80 °C; add to ice; Method B: CH_3SO_3H at 50 °C, heat to 80 °C; add to ice.

isatins were similar or slightly improved when methanesulfonic acid was used as the media.

In the case of the extremely insoluble aryl-containing examples such as **7p**, although heating in methanesulfonic acid produced isatins, uncharacterized impurities arising from the process were difficult to remove. The preparation of 5-tritylisatin (**16**) from 4-tritylaniline was chosen as the most difficult example for method modification. In order to further increase solubility in the acidic media and avoid these impurities, two modifications were employed: (1) the corresponding methyloximinoacetanilide, **15**, was utilized which was, in turn, prepared from acid **6c**[10] (Fig. 3), and (2) polyphosphoric acid (PPA) was used as the media. In this way, 5-tritylisatin (**16**) was produced in 67% yield.

The straightforward preparation of benzyl-, or in certain cases methyloximinoacetanilides (such as **7a–p, 15**) and the heating of these intermediates in sulfuric acid, methanesulfonic acid, or, for poorly soluble analogs PPA, has been shown to afford substituted isatins. This modified aniline-to-isatin route circumvents many of the problems present in the classical Sandmeyer isatin synthesis and allows production of these substituted isatins in a reproducible manner.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.035.

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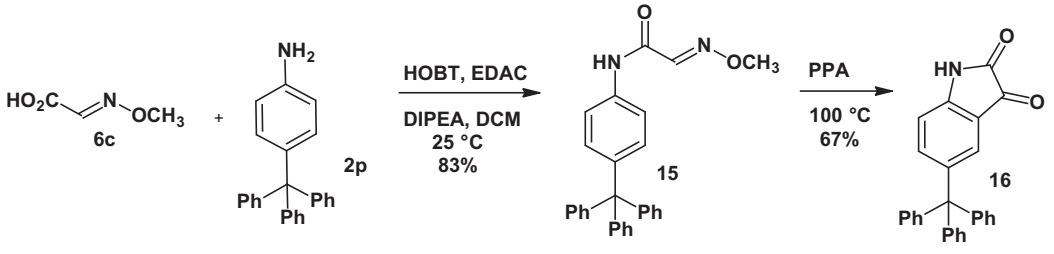

Figure 3. Synthesis of 5-tritylisatin (**16**).

Synth. Commun. **1999**, *29*, 3627–3633; (c) Mamun, H. M.; Foysal, M. A.; Mahabub, M.; Al-Amin *J. Sci. Res.* **2010**, *2*, 322–329.
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