



Anthranilic acids from isatin: an efficient, versatile and environmentally friendly method

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ABSTRACT

This paper describes the preparation of a series of 16 anthranilic acids in yields ranging from 51 to 97%, by treating the isatins with NaOH and H₂O₂. Independently of the nature of the substituent on the aromatic ring, the reactions were complete in 15 min at room temperature, whereas those of isatins containing a substituent on the nitrogen atom required longer reaction time for completion (45 min) under the same reaction conditions.

Key words: isatin, anthranilic acid, 2-aminobenzoic acid, isatin oxidation.

INTRODUCTION

Anthranilic acid or 2-aminobenzoic acid (1 - Fig. 1) is an intermediate metabolite for the production of the neurotransmitter serotonin (Mendoza et al. 2008). For playing a significant role in human lactation it is called vitamin L1, where the "L" stands for lactation, although it is not officially recognized as a vitamin (Wang and Okabe 2005).

Anthranilic acid was first described by Carl Julius Fritzsche (1808-1871) in the early XIX century when it was accidentally obtained from the degradation of indigo. Since then anthranilic acid has been used in the textile industry as a raw material for the production of dyes (Wiklund and Bergman 2006). It is target of various chemical transformations, such as alkylation or acylation reactions at the amino group, esterification and coupling with amines

at the carboxyl group and electrophilic aromatic substitution reactions (Wiklund and Bergman 2006, Naik et al. 2004, Hosangadi and Dave 1996, Mahiwal et al. 2012, Chaudhuri et al. 2007). Anthranilic acid and derivatives have applications in various sectors, including the food and perfumery industries, and are used in the syntheses of bioactive molecules (Wiklund and Bergman 2006). It is noteworthy that Ponstan[®] (mefenamic acid, used to relieve pain and inflammation) and Diurisa[®] (furosemide + amiloride hydrochloride, a diuretic association) have the anthranilic core. According to the literature, anthranilic acid exhibits anticancer, antimicrobial, insecticide, antiviral and anti-inflammatory activities (Huang et al. 2006, Lahm et al. 2007, Yadav and Krishnan 1998, Nittoli et al. 2007, Pajor and Sun 2013).

A few methods are available for the synthesis of unsubstituted anthranilic acid. Although yields are high, the reaction conditions are often severe

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and/or require the use of expensive reagents which need careful handling (Xu and Wolf 2009, Guin et al. 2007, Pandarus et al. 2011).

Substituted anthranilic acids can be obtained from the electrophilic aromatic substitution of anthranilic acid, or from the reaction of substituted isatins with NaOH and H₂O₂ (Popp 1975, Da Silva et al. 2001, Lisowski et al. 2000, Gérard et al. 2005). Although this method was described by Mayer and Schulze in 1925 (Mayer and Schulze 1925), no systematic study of this reaction has appeared in the literature. Herein we describe our studies of this reaction, starting from a number of isatins and varying the nature and position of the substituents in the aromatic ring or in the N-H group.

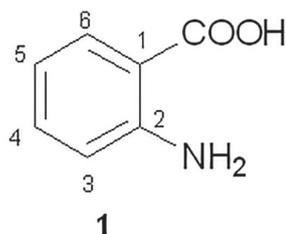


Figure 1 - Structure of anthranilic acid (1).

RESULTS AND DISCUSSION

All anthranilic acids were obtained in a single step from the reactions of substituted isatins with sodium

hydroxide (NaOH 5% w/w) and hydrogen peroxide (H₂O₂ 30% v/v). The products were isolated by filtration under vacuum after precipitation at pH between 1 and 3, as shown in Table I.

Yields ranged from 51 to 97 %. No significant difference was observed in the yields of the products upon varying the nature of the group or atom on the isatin ring (entries 1-11). In these cases, the reactions were left for 15 min. under stirring at room temperature, whereas those of isatins containing a substituent on the nitrogen atom required longer reaction times for completion (45 min.) under the same reaction conditions. Good yields of the products were also obtained in these cases.

An advantage of this method is that it allows the synthesis of anthranilic acids containing *ortho* or *meta* substituents to the amino group (entries 7-8). Oxidation of isatin has also proven to be efficient for the preparation of disubstituted anthranilic acids (entries 9-11), prepared otherwise by electrophilic substitution on the aromatic ring. The method also allows the preparation of alkyl- (entries 13-16) or acyl- (entry 12) *N*-substituted anthranilic acids. It should be noted that *N*-alkylation of isatins is a simple process (Wang et al. 2012, Garden et al. 1998), whereas anthranilic acid *N*-alkylation often requires drastic reaction conditions and the use of expensive catalysts (Hikawa and Yokoyama 2011).

TABLE I
Anthranilic acids obtained from isatin with their respective reaction times (in min), pH and yields (%).

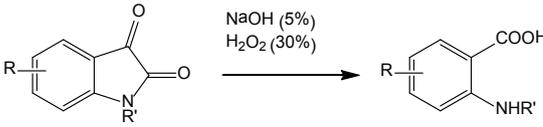
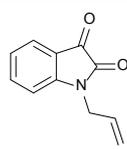
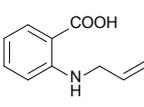
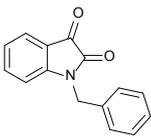
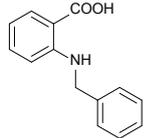
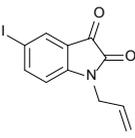
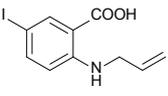
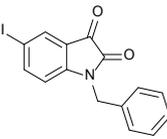
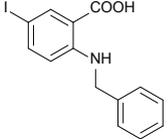
Entry	Substrate	Product	Reaction time	pH (pH of the reaction medium after addition of HCl)	Yield
1			15	2	75

TABLE I (continuation)

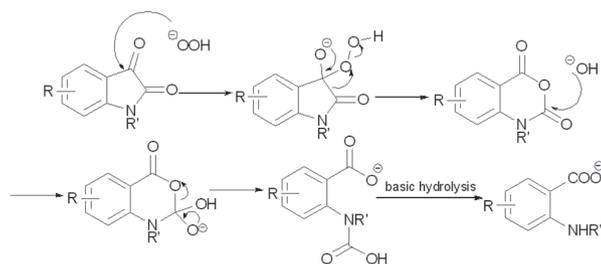
Reaction scheme showing the conversion of a substituted indole-2,3-dione (with R and R' substituents) to a substituted anthranilic acid (with COOH and NHR' substituents) using NaOH (5%) and H₂O₂ (30%).

Entry	Substrate	Product	Reaction time	pH (pH of the reaction medium after addition of HCl)	Yield
2			15	2	69
3			15	1	75
4			15	1	74
5			15	3	78
6			15	1	67
7			15	3	51
8			15	2	95
9			15	3	69
10			15	3	97
11			15	3	80
12			45	3	68

TABLE I (continuation)

					
Entry	Substrate	Product	Reaction time	pH (pH of the reaction medium after addition of HCl)	Yield
13			45	3	74
14			45	3	91
15			45	3	78
16			45	3	91

A mechanistic proposal for the isatin oxidation in the presence of H_2O_2 and NaOH is described in Scheme 1.



Scheme 1 - Mechanistic proposal for the isatin oxidation in the presence of H_2O_2 and NaOH .

CONCLUSION

This work shows the generality of the isatin oxidation method for the preparation of anthranilic

acids. The isatins used as starting materials may contain different substituents on the nitrogen atom or in the aromatic ring. This methodology offers the possibility to prepare different *N*-substituted anthranilic acids *via* simple alkylation and *N*-acylation reactions. Furthermore, all the products are obtained in short reaction times without catalysts and using aqueous basic solutions, featuring an environmentally friendly method.

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RESUMO

Este artigo descreve a preparação de uma série de 16 ácidos antranílicos, em rendimentos que variaram de 51 a 97%, através do tratamento de isatinas com NaOH e H₂O₂. Independentemente da natureza do substituinte no anel aromático, as reações se completaram em 15 min. a temperatura ambiente, ao passo que as isatinas contendo substituinte no átomo de nitrogênio requereram um tempo maior para completar a reação (45 min.), sob as mesmas condições.

Palavras-chave: isatina, ácido antranílico, ácido 2-aminobenzoico, oxidação da isatina.

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SUPPLEMENTARY MATERIAL

- NMR spectra (¹H and ¹³C), infrared and the typical procedure for preparation of the compounds (Experimental section).
- Figures 1-48.

