



Anais da Academia Brasileira de Ciências

ISSN: 0001-3765

aabc@abc.org.br

Academia Brasileira de Ciências

Brasil

RIO, GABRIEL F.; SILVA, BÁRBARA V.; MARTINEZ, SABRINA T.; PINTO, ANGELO C.

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

Anais da Academia Brasileira de Ciências, vol. 87, núm. 3, 2015, pp. 1525-1529

Academia Brasileira de Ciências

Rio de Janeiro, Brasil

Available in: <http://www.redalyc.org/articulo.oa?id=32742179005>

- How to cite
- Complete issue
- More information about this article
- Journal's homepage in redalyc.org

redalyc.org

Scientific Information System

Network of Scientific Journals from Latin America, the Caribbean, Spain and Portugal

Non-profit academic project, developed under the open access initiative



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

GABRIEL F. RIO, BÁRBARA V. SILVA,
SABRINA T. MARTINEZ and ANGELO C. PINTO

Instituto de Química-CT, Universidade Federal do Rio de Janeiro/UFRJ, Avenida Athos da Silveira Ramos, 149, Bloco A, 7º andar, Cidade Universitária, 21941-909 Rio de Janeiro, RJ, Brasil

Manuscript received on June 10, 2014; accepted for publication on November 4, 2014

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

Correspondence to: Bárbara V. Silva
E-mail: barbara.iq@gmail.com

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.

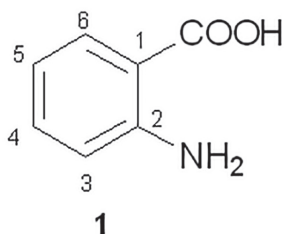


Figure 1 - Structure of anthranilic acid (1).

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)

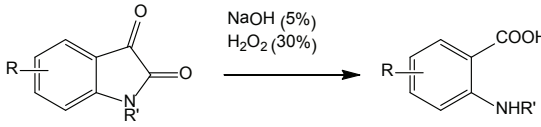
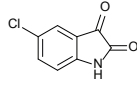
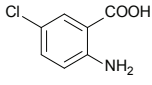
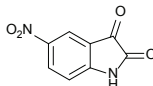
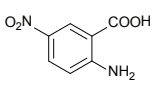
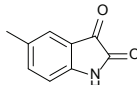
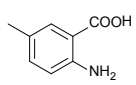
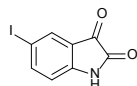
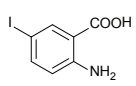
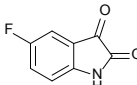
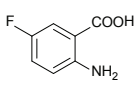
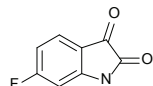
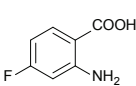
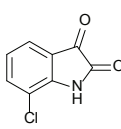
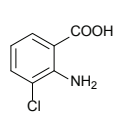
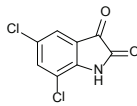
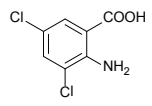
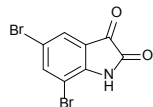
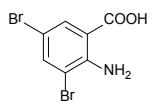
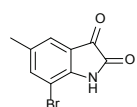
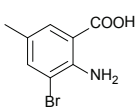
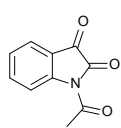
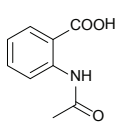
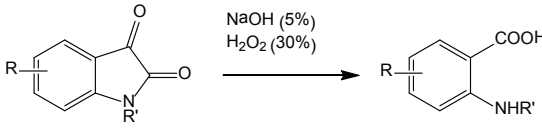
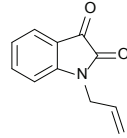
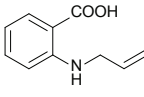
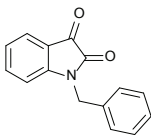
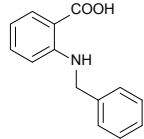
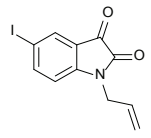
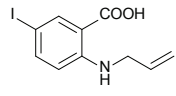
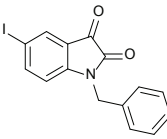
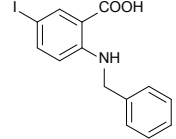
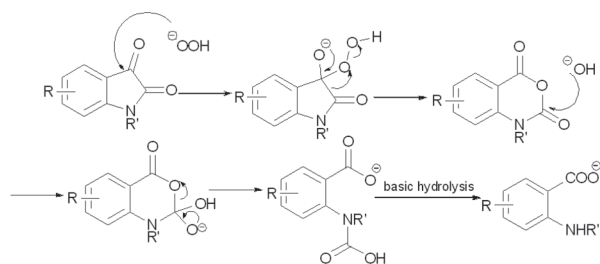
<div style="text-align: center;">  </div>					
Entry	Substrate	Product	Reaction time	pH (pH of the reaction medium after addition of HCl)	Yield
2			15	2	69
3			15	1	75
4			15	1	74
5			15	3	78
6			15	1	67
7			15	3	51
8			15	2	95
9			15	3	69
10			15	3	97
11			15	3	80
12			45	3	68

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.

ACKNOWLEDGMENTS

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for supporting the research.

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.

REFERENCES

- CHAUDHURI SK, ROY S, SAHA M AND BHAR S. 2007. Regioselective aromatic electrophilic bromination with dioxane dibromide under solvent-free conditions. *Synth Commun* 37: 579-583.
- DA SILVA JM, GARDEN SJ AND PINTO AC. 2001. The Chemistry of isatins: a review from 1975 to 1999. *J Braz Chem Soc* 12: 273-324.
- GARDEN SJ, TORRES JC, SILVA LE AND PINTO AC. 1998. A convenient methodology for the *N*-alkylation of isatin compounds. *Synth Commun* 28: 1679-1689.
- GÉRARD AL, LISOWSKI V AND RAULT S. 2005. Direct synthesis of new arylanthranilic acids via a Suzuki cross-coupling reaction from iodoisatins. *Tetrahedron* 61: 6082-6087.
- GUIN D, BARUWATI B AND MANORAMA SV. 2007. Pd on amine-terminated ferrite nanoparticles: a complete magnetically recoverable facile catalyst for hydrogenation reactions. *Org Lett* 9: 1419-1421.
- HIKAWA H AND YOKOYAMA Y. 2011. Palladium-catalyzed mono-*N*-allylation of unprotected anthranilic acids with allylic alcohols in aqueous media. *J Org Chem* 76: 8433-8439.
- HOSANGADI BD AND DAVE RH. 1996. An efficient general method for esterification of aromatic carboxylic acids. *Tetrahedron Lett* 37: 6375-6378.
- HUANG ST, HSEI IJ AND CHEN C. 2006. Synthesis and anticancer evaluation of bis(benzimidazoles), bis(benzoxazoles), and benzothiazoles. *Bioorg Med Chem* 14: 6106-6119.
- LAHM GP ET AL. 2007. RynaxypyrTM: A new insecticidal anthranilic diamide that acts as a potent and selective ryanodine receptor activator. *Bioorg Med Chem Lett* 17: 6274-6279.
- LISOWSKI V, ROBBA M AND RAULT S. 2000. Efficient synthesis of novel 3-(het)arylanthranilic acids via a Suzuki cross-coupling reaction of 7-iodoisatin with (het)arylboronic acids in water. *J Org Chem* 65: 4193-4194.
- MAHIWAL K, KUMAR P AND NARASIMHAN B. 2012. Synthesis, antimicrobial evaluation, ot-QSAR and mt-QSAR studies of 2-amino benzoic acid derivatives. *Med Chem Res* 21: 293-307.
- MAYER F AND SCHULZE R. 1925. Über das 4- und 6-Methylisatin. *Ber Dtsch Chem Ges* 58: 1465-1469.
- MENDOZA JLH, VELÁSQUEZ JDQ, MEDINA VRM AND PERÉZ NM. 2008. Biosíntesis de ácido antranílico y ácido indolacético a partir de triptófano en una cepa de *Azospirillum brasilense* nativa de Tamaulipas. *Avances en Investigación Agropecuaria* 12: 57-67.
- NAIK S, BHATTACHARJYA G, TALUKDAR B AND PATEL BK. 2004. Chemoselective acylation of amines in aqueous media. *Eur J Org Chem* 2004: 1254-1260.
- NITTOLI T ET AL. 2007. Identification of anthranilic acid derivatives as a novel class of allosteric inhibitors of hepatitis C NS5B polymerase. *J Med Chem* 50: 2108-2116.
- PAJOR M AND SUN NN. 2013. Nonsteroidal anti-inflammatory drugs and other anthranilic acids inhibit the Na⁺/dicarboxylate symporter from *Staphylococcus aureus*. *Biochemistry* 52: 2924-2932.
- PANDARUS V, CIRIMINNA R, BÉLAND F AND PAGLIARO M. 2011. Selective hydrogenation of functionalized nitroarenes under mild conditions. *Catal Sci Technol* 1: 1616-1623.
- POPP PD. 1975. The chemistry of isatin. *Adv Heterocycl Chem* 18: 1-58.
- WANG Y AND OKABE N. 2005. Crystal structures and spectroscopic properties of zinc (II) ternary. *Chem Pharm Bull* 53: 645-652.
- WANG Y, ZHANG M, CAO S, LIN H, GAO M AND LI Z. 2012. Synthesis of 1-substituted 4(1H)-quinazolinones under solvent-free conditions. *Synth Commun* 42: 2715-2727.
- WIKLUND P AND BERGMAN J. 2004. Alkylation and acylation of basic salts of anthranilic acid. *Tetrahedron Lett* 45: 969-972.
- WIKLUND P AND BERGMAN J. 2006. The chemistry of anthranilic acid. *Curr Org Synth* 3: 379-402.
- XU H AND WOLF C. 2009. Efficient copper-catalyzed coupling of aryl chlorides, bromides and iodides with aqueous ammonia. *Chem Commun* 21: 3035-3037.
- YADAV GD AND KRISHNAN MS. 1998. An ecofriendly catalytic route for the preparation of perfumery grade methyl anthranilate from anthranilic acid and methanol. *Org Proc Res Dev* 2: 86-95.

SUPPLEMENTARY MATERIAL

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

