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Article

Improved Method for Microwave-Assisted Synthesis of Benzodiazepine-2,5-diones from Isatoic Anhydrides Mediated by Glacial Acetic Acid

Armando De La Cruz,[a] Carlos Alejandro Vega-Acevedo,[a] Ignacio A. Rivero,[a] and Daniel Chávez*,[a]*

[a]*Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana, Apartado Postal 1166, 22000 Tijuana, BC, México*

An improved and simpler method for the synthesis of benzodiazepin-2,5-diones and 7-iodobenzodiazepin-2,5-diones catalyzed by glacial acetic acid using isatoic anhydride and 6-iodoisatoic anhydride, respectively, as starting materials is reported. The target products were achieved in good yields (up to 71%) using microwave irradiation as the activating mode of reaction in the presence of acetic acid instead of the traditional polar aprotic solvents as dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or dimethylacetamide (DMAC). Moreover, relatively simple purification workup is required. The optimal temperature to obtain the benzodiazepin-2,5-dione derivatives was 130 °C, while the best irradiation time was 3 min. In addition, the methodology for the selective preparation of 6-iodoisatoic anhydride with an overall yield of 62% is presented.

Keywords: benzodiazepin-2,5-diones, 7-iodobenzodiazepin-2,5-diones, microwave irradiation, isatoic anhydride, 6-iodoisatoic anhydride

Introduction

Benzodiazepines constitute an important class of biologically active compounds that have been studied in recent years.[1] Some members of this class have been identified as platelet aggregation inhibitors,[2] anticonvulsant agents,[3] antitumor compounds[4] and anxiolytic compounds.[5]

Benzodiazepines are synthesized from a benzodiazepin-2,5-dione precursor. Most of the synthetic methods of benzodiazepin-2,5-dione are based almost exclusively on the condensation of anthranilic acid and an amino acid or its derivatives, and several alkylating agents.[6,7] A variation of this method is the use of isatoic anhydride (**1**) instead of anthranilic acid with very similar results.[8-11]

Benzodiazepin-2,5-dione have been synthesized using solid phase approach, however, this method has some limitations; for example, the alkylation on the nitrogen of an amide reduces the number of alkylating agents available.[12-17] The use of microwave irradiation as activating mode for the synthesis of organic compounds[18] has increased considerably in recent times. It reduces reaction times considerably, the reactions are cleaner and the purification workup is simpler. In our research group, we have synthesized a variety of organic compounds, using microwaves with excellent results, such as alkylation of carboxylic acids and phenols[19] and 2,4-(1*H*,3*H*)-quinazolinediones,[20,21] and synthesis of hydropyridines.[22]

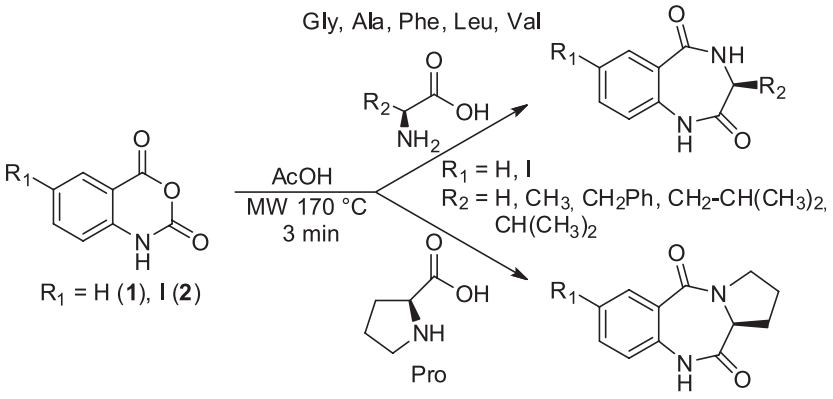
The goal of this study is to improve yields on the synthesis of benzodiazepin-2,5-dione derivatives with either isatoic (**1**) anhydride or 6-iodoisatoic anhydride (**2**) as starting materials, and their condensation with α-amino acids using microwave irradiation as activating mode and acetic acid as a polar protic solvent, as shown in Scheme 1.

Experimental

General procedures

Thin-layer chromatography (TLC) was performed on silica gel F254 plates (Merck). All compounds were detected using UV light. Melting points were obtained on an Electrothermal 88629 apparatus and are uncorrected. Infrared spectra (IR) were recorded on a PerkinElmer FT-IR 1600 spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained on either a Varian Mercury 200 MHz Spectrometer at 200 and 50 MHz, respectively, or a Bruker Avance III spectrometer at 400 and 100 MHz, respectively. ^{1}H and ^{13}C NMR spectra were recorded in

*e-mail: irivero@tectijuana.mx; dchavez@tectijuana.mx



Scheme 1. Synthesis of benzodiazepin-2,5-dione derivatives.

$CDCl_3$, DMSO-d_6 or CD_3OD with tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on an Agilent Technologies 5975C MS Spectrometer at 70 eV by direct insertion. Optical rotations were determined using a Rudolph Research Analytical automatic polarimeter. Microwave equipment was a self-tuning single mode CEM DiscoverTM Focused Synthesizer.

General method for preparing benzodiazepine-2,5-diones (**3**-**14**)

In a microwave vial with a capacity of 10 mL, it was mixed isatoic anhydride (**1**) or 6-iodoisatoic anhydride (**2**) (10 mmol), the corresponding α-amino acid (10 mmol) and 3 mL of glacial. The reaction was carried out at 130 °C for 3 min. After irradiation, the reaction mixture was cooled to room temperature forming a precipitate, which was filtered, washed three times with hot water and filtered under vacuum to give the products **3**-**14** as solids. The percentage recoveries were between 61-71%.

Procedure for the synthesis of 6-iodoisatoic anhydride (**1**)

Methyl anthranilate (**15**) (2.0 g, 13.2 mmol), granulated iodine (3.36 g, 13.2 mmol) and hydrogen peroxide-urea (1.24 g, 13.2 mmol), were dissolved in 20 mL of ethyl acetate. The reaction mixture was stirred for 1.5 h at room temperature and then washed with sodium thiosulfate (3 × 10 mL) and water (3 × 10 mL); then solvent was evaporated under reduced pressure to afford methyl 2-amino-5-iodobenzoate (**16**) as a brown solid (3.33 g, yield 91%). The solid was hydrolyzed using NaOH/MeOH (5%) to give 2-amino-5-iodobenzoic acid (**17**) (2.81 g, yield 89%). Finally, the acid was cyclized with triphosgene and triethylamine as base affording 6-iodoisatoic anhydride (6-iodo-1*H*-benzo[*d*][1,3]oxazine-2,4-dione, **2**) with a 76% yield (2.34 g).

Results and Discussion

The synthesis of benzodiazepin-2,5-dione derivatives was carried out using microwave irradiation as the activating mode of reaction, employing isatoic anhydride (**1**) and six α-amino acids with a hydrophobic side chain as glycine, alanine, proline, phenylalanine, leucine and valine, as starting materials, to afford compounds **3**-**8**, respectively (Figure 1). In order to improve the yield of the reaction, we evaluate different microwave irradiating times and different heating temperatures, as well as the use of glacial acetic acid, as a protic solvent, instead of the traditional dimethylformamide (DMF), dimethyl sulfoxide (DMSO) or dimethylacetamide (DMAC), or 2-methoxyethanol. The use of these non-protic solvents have been reported previously in the condensation of acyclic α-amino acids with isatoic anhydride, resulting in low yields (up to 25%).[10]

The condensation of isatoic anhydride (**1**) and α-amino acids was evaluated considering four different times (1, 3, 5, and 7 min) and five temperatures (90, 110, 130, 150 and 170 °C) (Table 1). After irradiation, treatment of each reaction mixture consisted in allowing the reaction to cool to room temperature with formation of a precipitate. The precipitate was filtered, washed three times with hot water, dried under vacuum and then analyzed by TLC and gas chromatography-mass spectrometry (GC-MS).

When irradiation time was only 1 min, unreacted isatoic anhydride (**1**) was detected on all runs. Similar results were obtained at 90 and 110 °C. Condensation of isatoic anhydride (**1**) with the α-amino acids at 150 and 170 °C and longer times than 3 min, resulted mainly in formation of the open dimer and trimer from the isatoic anhydride (**1**). Therefore, the optimal temperature to obtain the products **3**-**8** was 130 °C, while the best irradiation time was 3 min (Table 1). We also try, under the same conditions, condensation of isatoic anhydride (**1**) and two charged α-amino acids, lysine and aspartic acid, but benzodiazepin-

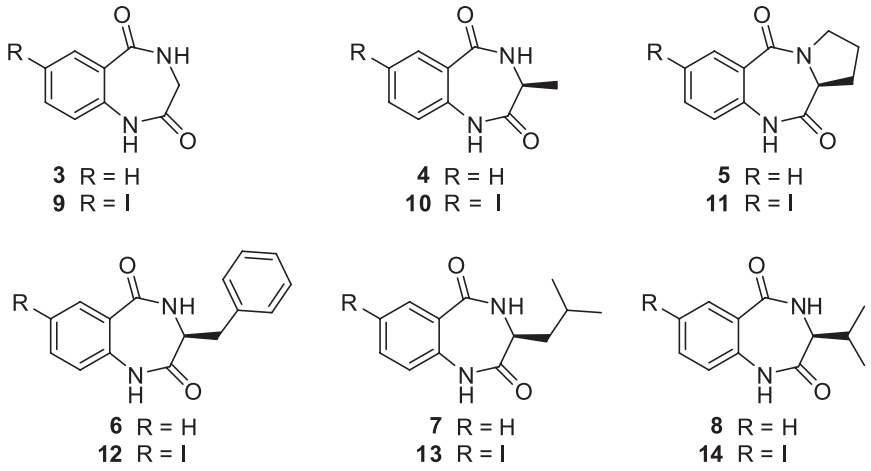


Figure 1. Structures of benzodiazepin-2,5-diones (**3**-**14**).

Table 1. Conditions used for obtaining benzodiazepin-2,5-diones **3**-**8**, and yields

Reaction time / min	Condition, yield / %				
	90 °C	110 °C	130 °C	150 °C	170 °C
1	ND	ND	ND	< 10%	< 10%
3	< 10%	< 10%	61-71%	< 20% dimer + trimer	ND dimer + trimer
5	< 10%	< 10%	< 20% dimer + trimer	ND dimer + trimer	ND dimer + trimer
7	< 10%	< 10%	ND dimer + trimer	ND dimer + trimer	ND dimer + trimer

ND: benzodiazepin-2,5-diones not detected; dimer: 2-(2-aminobenzamido)benzoic acid; trimer: 2-(2-(2-aminobenzamido)benzamido)benzoic acid.

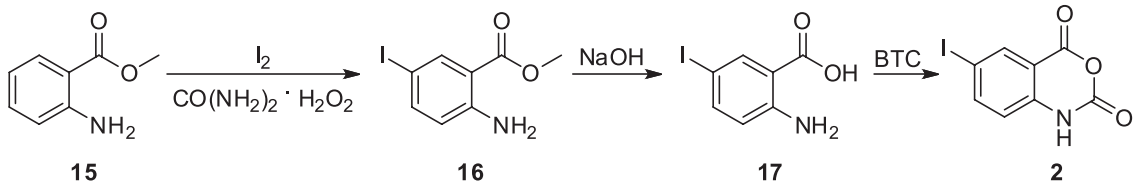
2,5-diones were not obtained, instead only open dimer and trimer from the isatoic anhydride were detected.

The synthesis of benzodiazepin-2,5-diones **3**-**8** was achieved with good yields (61 to 71%), with very simple purification procedures. Benzodiazepin-2,5-diones **3**-**8** were identified by comparison of IR, NMR, and electron impact mass spectrometry (EIMS) data with those published in the literature.[9-11,15,23] As mentioned above, benzodiazepines participate in important biological activities, and analogues with groups, such as iodine in the aromatic system would modify the structure and, consequently, their properties will be affected. Preparation of new molecules with improved properties is of current importance. Therefore, including halides in the aromatic system, in particular iodine, results in very important intermediates for the synthesis of more complicated molecules, since it allows a wide range of reactions such as Sonogashira,[24] Suzuki,[25] Stille,[26] Heck,[27] Hiyama,[28] Negishi,[29] etc. Preparation of compounds with groups such as iodine are of a high synthetic value and a wide variety of reactions can be performed. Therefore, the synthesis of 7-iodobenzodiazepin-2,5-diones derivatives was proposed.

In order to use the previous methodology, it was necessary to synthesize 6-iodoisatoic anhydride (**2**). Using 2-aminobenzoic acid and hydrogen peroxide-urea led to no product formation. However, when methyl anthranilate (**15**) was used, methyl 2-amino-5-iodobenzoate (**16**) was obtained, with a 91% yield. Basic hydrolysis gave 2-amino-5-iodobenzoic acid (**17**) and finally cyclization with triphosgene bis(trichloromethyl) carbonate (BTC) afforded 6-iodoisatoic anhydride (**2**) with an overall yield of 62% (Scheme 2).

Following the same procedure as for **3**-**8** (130 °C, 3 min), condensation of 6-iodoisatoic anhydride (**2**) and the six α-amino acids, using glacial acetic acid, lead to the 7-iodobenzodiazepin-2,5-diones **9**-**14**, with similar yields (65 to 70%), and simple purification workup.

Optical rotation obtained from products **4**-**8** and **10**-**14** indicated that no isomerization on the chiral center coming from α-amino acids via enol-form occurred. Thus, the proposed method to obtain benzodiazepin-2,5-diones **3**-**8** and 7-iodobenzodiazepin-2,5-diones **9**-**14**, mediated by glacial acetic acid and using microwave irradiation, shows a good improvement to the traditional use of DMSO as



Scheme 2. Synthesis of 6-iodoisatoic anhydride (**2**).

solvent. Comparison of yields published by Jadidi *et al.*[10] on obtaining benzodiazepin-2,5-diones **3**, **4**, **6** and **7**, showed that irradiation at 130 °C for 3 min results in better yields than irradiation at full power (600 W) for 7 min (Table 2). Also, the corresponding 7-iodobenzodiazepin-2,5-diones **9**, **10**, **11** and **13**, were obtained with good yields.

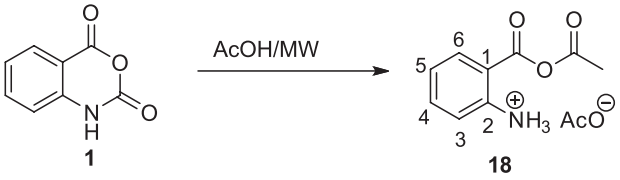
Table 2. Comparison of yields using DMSO or ACOH in the condensation of acyclic α-amino acids with isatoic anhydride

Compound	Yield[a] / %	Yield[b] / %	Compound	Yield[a] / %
3	62	20	**9**	68
4	65	25	**10**	70
5	np	68	**11**	69
6	71	15	**12**	65
7	69	20	**13**	70
8	np	61	**14**	69

[a]AcOH, 130 °C, 3 min; [b]DMSO, 600 W, 7 min, obtained from the publication.[10] np: data not published in reference 10.

The good yields obtained (up to 71%) on the condensation of isatoic anhydride (**1**) or 6-iodoisatoic anhydride (**2**) with α-amino acids, via microwave irradiation, were achieved when glacial acetic acid was used as a solvent. It is clear that the role of acetic acid is not only as a solvent, but facilitates the reaction, perhaps forming a more reactive intermediate, like a mixed anhydride.

In order to support this proposal with experimental evidence, in a microwave vial it was added isatoic anhydride (**1**) and glacial acetic acid and irradiated at 130 °C for 3 min. After the mixture was cooled, the NMR spectra were obtained. In addition to the signals for the isatoic anhydride and acetic acid, a new set of NMR signals were detected, at δ_H 8.53 (d, *J* 7.6 Hz, H-3), 8.00 (dd, *J* 7.9, 1.6 Hz, H-6), 7.55 (ddd, *J* 7.9, 7.6, 1.6 Hz, H-5), 8.53 (ddd, *J* 7.6, 7.6, 1.3 Hz, H-4), 2.16 (s, C$\underline{H}_3$) and δ_C 170.9 (C=O), 169.9 (C=O), 142.4 (C-2), 135.2 (C-4), 132.4 (C-6), 123.6 (C-5), 121.0 (C-3), 117.3 (C-1), 26.0 (C$\underline{H}_3$), which can be attributed to the acetic 2-aminobenzoic anhydride (**18**). Therefore, when glacial acetic acid is used, the mixed anhydride **18** is formed (Scheme 3), which is a more reactive intermediate, increasing yields in the condensation of acyclic α-amino acids with isatoic anhydride.



Scheme 3. Feasible formation of mixed anhydride.

Conclusions

We are presenting an easy, efficient and improved method to obtain benzodiazepin-2,5-diones and 7-iodobenzodiazepin-2,5-diones, catalyzed by glacial acetic acid, using microwave irradiation as the activating mode of reaction. The synthesis is carried out with inexpensive reagents and short reaction times compared to traditional methods. Purification required washing the reaction mixture with hot water and dried *in vacuo*. This method provides good yields, up to 71%, on the preparation of benzodiazepin-2,5-dione derivatives which may be attributed to the use of acetic acid as solvent, possibly forming a mixed anhydride which is a more reactive intermediate.

The methodology for the selective synthesis of 6-iodoisatoic anhydride (**2**) with a global yield of 62% is also presented.

Supplementary Information

Supplementary information (spectroscopic data, ^{1}H NMR and ^{13}C NMR spectra and mass spectra (EI)) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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