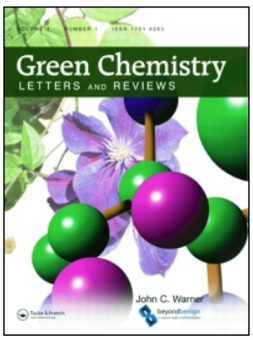

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Green, lithium salt-free synthesis of 2-alkylated 1,4-benzenediols in hydroalcoholic media

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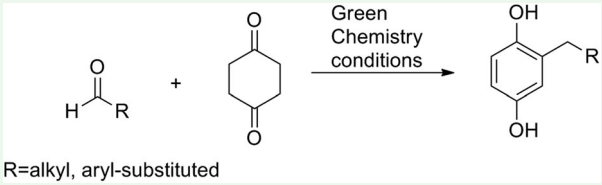
ABSTRACT

Herein, we describe an efficient, green, and lithium salt-free synthesis of 2-substituted 1,4-benzenediol in water/ethanol as solvent and potassium carbonate as a base. Optimized reaction time, the required equivalent of base and the observed solvent effect are reported.



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KEYWORDS
Hydroalcoholic media; lithium salt free; green method

Introduction

The synthesis of biologically active new compounds is still one of the main challenges of modern organic chemistry (*1*). Particularly, polyphenols have been widely used as antioxidant, antitumoral and antiparasitic drugs, among other uses (*2–4*). 2-alkyl-1,4-Benzenediols derivatives have attracted attention as there are few references available about their preparation and potential biological activity (*5*). Usually, these compounds were synthesized via Friedel–Crafts alkylation (*6*) of hydroquinone, which have various drawbacks such as polyalkylation, rearrangement reaction and the use of toxic or hazardous reagents (*7*, *8*).

In 1997, Ozaki and co-workers (*9–11*) published a synthesis of this type of compounds starting with 1,4-cyclohexanedione and several alkylaldehydes in 1,3-dimethyl-2-imidazolidinone (DMI) as the solvent in the presence of lithium chloride at 160°C. The use of no "green" solvents and troublesome work-up as well as the use of lithium salts and extreme temperature make these conditions inappropriate for a large-scale process. Based on green chemistry principles herein, we disclose a new synthetic method for the preparation of 2-alkylated 1,4-benzenediols (*12*). This strategy involves a tandem aldolic condensation/isomerization/aromatization between the diketone and the selected aldehyde. The aldolic condensation under basic conditions is followed by an isomerization of the exocyclic alpha-beta unsaturated ketone moiety to the more stable aromatic derivative 2-substituted 1,4-benzenediol (Figure 1). Using our method we synthesize a library of 2-subtituted-1,4-benzenediols to assay their activity against *Leishmania* sp. and to complete their structure–activity relationship studies (Figure 2) (*13*, *14*).

Results and discussion

Synthesis of 2-benzyl 1,4-benzenediol (3)

The reactions between 1,4-cyclohexanedione (**1**) and benzaldehyde (**2**) (Figure 3) were carried out using K_2CO_3 in the presence of catalytic amount of crown ether (18-crown-6) under different experimental conditions as shown in Table 1. In the course of our study, we examined different parameters such as solvent, temperature and reaction time as well as different molar ratios between **1**, **2** and K_2CO_3. We obtained low yields under solvent-free conditions (entry 1) or in water as a solvent under reflux (entries 2, 3, and 4). We suggest that these results are affected by poor solubility of benzaldehyde in water and the decomposition of the reagents in the presence of

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Supplemental data for this article can be accessed here.10.1080/17518253.2016.1238966

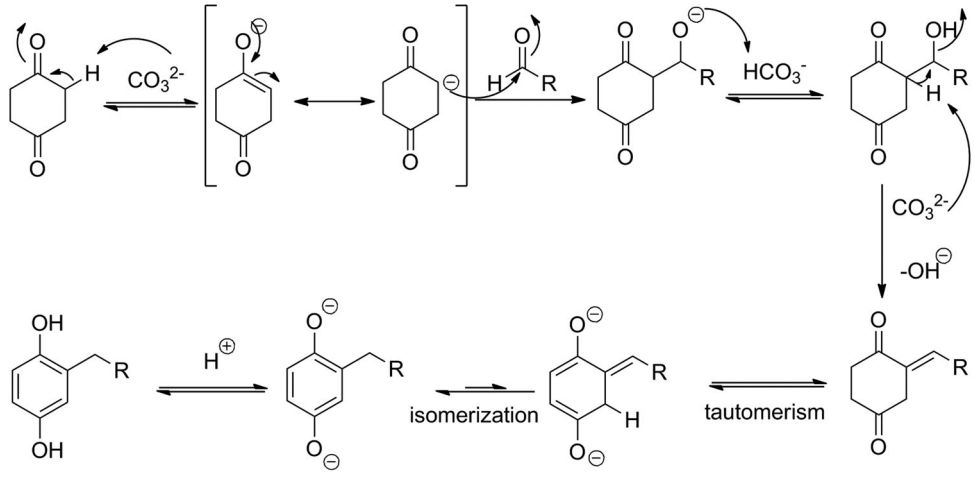


Figure 1. Proposed mechanism for the reaction under the green chemistry condition.

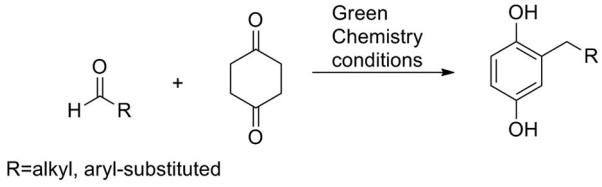


Figure 2. Preparation of 2-alkylated 1,4-benzenediols according green chemistry principles.

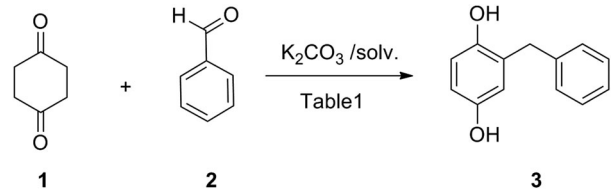


Figure 3. Reaction of 1,4-cyclohexanedione (**1**) with benzaldehyde (**2**).

base at reflux. However, when the reaction was performed at room temperature, better yield was achieved (66%). Longer reaction time did not lead to higher conversion as the crude contained significant quantity of impurities. When two equivalents of **1** were used to react in H_2O/EtOH (9:1) as a solvent, poor yield was obtained (entry 6), whereas excess of benzaldehyde was a more efficient condition (entry 7). Further studies revealed that if the reaction was performed at reflux, 18-crown-6 ether was not necessary. Also, the addition of benzaldehyde in 4 portions for every 15 min improved the outcome of the desired product yielding 84% (entry 8), reaching the yield reported by Ozaki (*9*) for this compound. Hence, we decided to use this optimized conditions for the syntheses of 2-alkyl-1,4-benzenediol derivatives.

Synthesis of halogen derivatives (5a–5f)

Expanding the scope of this environmentally benign protocol we selected commercially available monohalogenated benzaldehydes (Table 2, entries **5a–5f**) as reaction partner of 1,4-cyclohexanedione (**1**). We obtained good yields with both chlorobenzaldehydes (**5a–5b**) but lower with fluoro (**5c–5d**) and *para*-bromo derivatives (**5e**). Refluxing for longer time leaves the yield unchanged. Surprisingly compound

Table 1. Reaction conditions between 1,4-cyclehexanedione (**1**) and benzaldehyde (**2**).[a]

Entry	**1** (eq)	**2** (eq)	K_2CO_3 (eq)	Solvent	Time (h)	Temp. (°C)	Yield (%)
1	1	2	1	Solvent free	1.5	Reflux	31
2	1.1	1	1.2	H_2O	1.5	Reflux	25
3	1	4	1.2	H_2O	1.5	Reflux	30
4	2	1	1	H_2O	0.5	Reflux	25
5	1	4	1.2	H_2O	21	R.T.	66
6	2	1	1	H_2O/EtOH (9:1)	0.5	Reflux	45
7	1	2	1	H_2O/EtOH (9:1)	2.5	Reflux	71
8[b]	1	2	1	H_2O/EtOH (9:1)	1.5	Reflux	84

[a]Catalytic amount of ether 18-crown-6 was added in all cases.
[b]No ether 18-crown-6 needed and benzaldehyde was added in 4 portions every 15 min.

Table 2. Yields and reaction times for the preparation of halobenzaldehydes derivatives.

Compound	X	Time (h)	Yield (%)
5a	4-Cl	0.25	72
5b	3-Cl	1.00	73
5c	4-F	1.25	50
5d	2-F	1.00	45
5e	4-Br	0.25	51
5f	2-Br	3.00	82

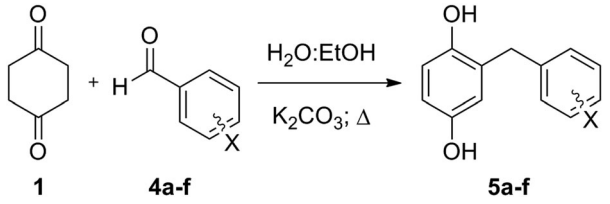


Figure 4. Synthesis of haloderivatives.

5f was obtained in 82% yield after 3 h of reaction (Figure 4).

Synthesis of hydroxy and methoxy analogs

To explore the scope and limitations of this new protocol, a wide range of substituted hydroxy- and methoxybenzaldehydes (Figure 5) were reacted with cyclohexanedione (**1**) under the optimized conditions (see Table 3). This study revealed that free hydroxyl groups contribute to diminish the outcome in spite of the excess of base used in comparison with methoxybenzaldehydes derivatives (**7f– 7i**) (*15, 16*). *para*-Hydroxyl-substituted benzaldehydes (products **7a** and **7e**) showed the highest reaction times as the electron-donating effect decreases the reactivity of the carbonyl to nucleophilic attack.

Preparation of analogues possessing EDG and EWG substituents

We continued testing different substituted benzaldehydes bearing either electron-donating or withdrawing groups as reagents (Figure 6). Except for *p*-nitrobenzaldehyde (**9i**) which decomposed during the reaction, all the other aromatic aldehydes containing

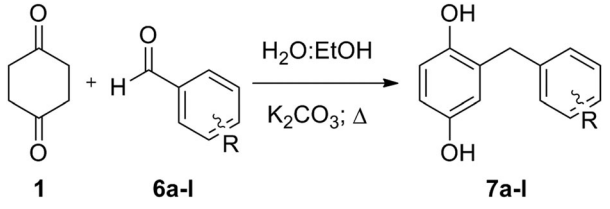


Figure 5. Reaction of 1,4-cyclohexanedione (**1**) with benzaldehydes possessing hydroxy or methoxy substituents.

Table 3. Yields and reaction times for the preparation of hydroxy and methoxybenzaldehydes derivatives.

Compound	R[a]	Time (h)	Yield (%)
7a	4-OH	9.00	50
7b	3-OH	3.00	32
7c	2-OH	4.50	79
7d	2,5-$(OH)_2$	1.50	73
7e	3,4-$(OH)_2$	12.00	51
7f	4-OMe	4.00	92
7g	3-OMe	1.50	60
7h	2-OMe	1.00	73
7i	3,4-methylendioxy	1.75	87
7j	3,4,5-$(OMe)_3$	1.00	43
7k	2,4,6-$(OMe)_3$	1.00	81
7l	3-OH-4-OMe	2.50	41

[a]When R=OH an extra equivalent of K_2CO_3 per hydroxyl was required.

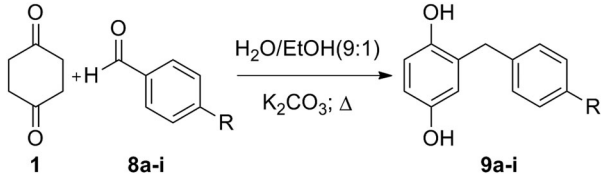


Figure 6. Reaction of 1,4-cyclohexanedione (**1**) with benzaldehydes possessing EDG and EWG substituents.

Table 4. Yields and reaction times for the preparation analogues with EDG and EWG substituents.

Compound	R	Time (h)	Yield (%)
9a	CH_3	1.00	72
9b	Ph	4.00	58
9c	NMe_2	3.00	38
9d	NHAc	2.50	70
9e	CHO	3.00	68
9f	COOH	3.00	46
9g	CF_3	1.00	93
9h	CN	0.50	92
9i	NO_2	0.25	Decomposition

EDG or EWG gave moderate to good yields of the corresponding products (Table 4; **9a–9h**).

Synthesis of alkyl and aryl derivatives of 3

When assaying alkyl aldehydes of different chain lengths and ramifications (Figure 7) we observed that yield increases in the case of medium length chains such as **11b** and **11c,** but decreases with shorter aldehydes such as formaldehyde and longer aldehydes such as nonanal (Table 5 entries **11a–11g**) (*9, 15, 17–20*). This can be explained by two reasons: the poor solubility of nonanal in the solvent mixture and the use of paraformaldehyde for the synthesis of 2-methyl-1,4-benzenediol (**11a**). Degradation of formaldehyde under

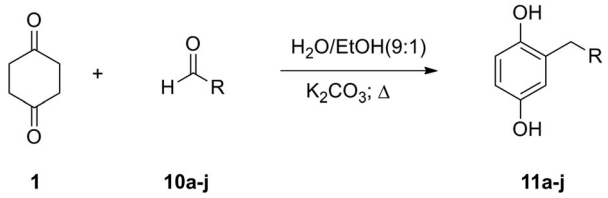


Figure 7. Synthesis of 2-(alkyl or aryl)-1,4-benzenediol derivatives.

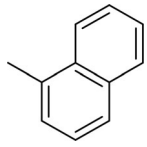
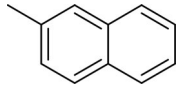
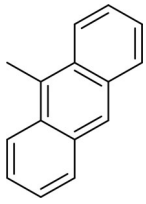
alkaline conditions results in a decrease of the final product (*21*).

We had previously developed a synthetic method involving a Wittig reaction for the synthesis of **11b** and **11g** in three steps affording 28% and 36% overall yield, respectively (*14*). This fact clearly proves the advantages of the present "green" method compared with the traditional ones. We were able to reduce number of steps with better yields (86% and 90% for **11b** and **11g,** respectively) that resulted in safer conditions, reagents and solvents. We also tested polycyclic aromatic aldehydes (entries **11h-11j**) with similar yields but longer reaction time for **11j**, probably due to its very high lipophilicity (*15*, *21*).

Synthesis of 2-substituted 1,4-benzenediol dimers

Finally, we used this methodology to obtain dimers **14** and **15** (Figure 8) using 4-terephthalaldehyde (**12**) and 4-(4-formylphenoxy)benzaldehyde (**13**) along with 2 equivalents of **1** and K_2CO_3. Both products had similar yields but surprisingly **15** needed longer reaction time than **14**.

Table 5. Yields and reaction times for the preparation of 2-(alkyl or aryl)-1,4-benzenediol derivatives.

Entry	R	Time (h)	Yield (%)
11a	–H	3.00	36
11b	$-C_4H_{11}$	3.00	86
11c	$-C_5H_{11}$	4.00	62
11d	$-C_8H_{17}$	3.00	41
11e	$-CH(CH_3)_2$	3.50	58
11f	–Cy	2.50	64
11g	$-CH_2Ph$	1.00	90
11h		1.00	61
11i		1.00	56
11j		6.00	58

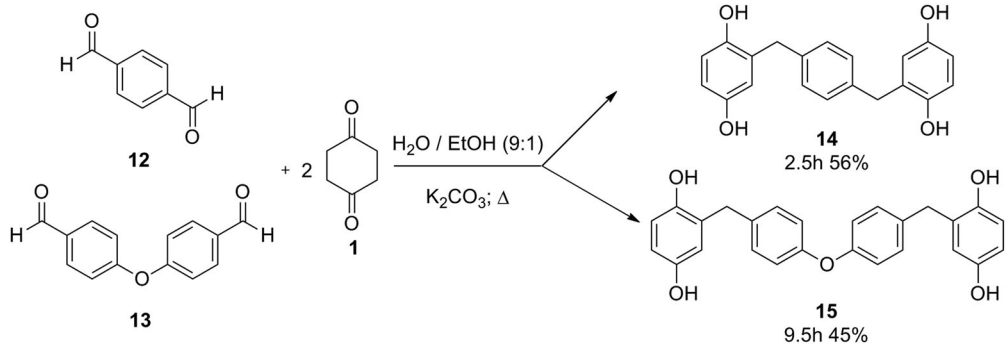


Figure 8. Synthesis, yield and reaction times for the preparation of dimers **14** and **15.**

Conclusions

In summary, we have developed a new green method for the synthesis of 2-alkyl-1,4-benzenediols using1,4-cyclohexanedione and a variety of alkyl and aryl aldehyde in hydroalcoholic medium and K_2CO_3 as a base under reflux. Reaction times were short (under 4 h) in the majority of cases, with the exception of 3,4-dihydroxybenzaldehyde which needed 12 h to reach completion. We assayed several alkyl and arylaldehydes with a wide variety of substituents, including electron-donor and electron-acceptor groups. Moderate to excellent yields were obtained with a broad substrate scope. The reaction only failed with nitro substrates.

Therefore, the proposed green and simple preparation of 2-alkylated-1,4- benzenediols derivatives allowed us to prepare a library of potentially biologically active compounds.

Experimental

General experimental procedure

A solution of K_2CO_3 (1 mmol) in a water ethanol 9:1 mixture (20 mL) is heated with stirring. Once the solution is under reflux, 1,4-cyclohexanedione (1 mmol) is added slowly. Afterwards, selected aldehyde (2 mmol) is added slowly in 4 portions every 15 min. When the reaction is completed (monitored by TLC), HCl 10% solution is added dropwise while still hot, until neutral (especially with amphotheric compounds) or slightly acidic pH. The aqueous solution is extracted 3 times with ethyl acetate and the collected organic layer is washed with brine, dried under Na_2SO_4 and evaporated *in vacuo*. Purification is performed by column chromatography (AcOEt/ Hex; 1/1)

In the case of free phenolic aldehyde (**6a**–**6e** and **6l**) and carboxylic acids substituent (**8f**), an extra equivalent of base per acidic proton was used.

For the synthesis of dimers **14** and **15**, two equivalents of cyclohexanedione and base were used per equivalent of aldehyde.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Notes on contributors

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Natali Graziano worked as research assistant at the Departamento de Química Orgáníca until she obtained her degree. Actually, she works for an agrochemical company.

Enrique Pandolfi received his MSc title Chemistry from the Facultad de Química, Universidad de la República under the supervision of Prof. Patrick Moyna. He moved to Germany to continue his doctoral studies with a DAAD scholarship at the University of Saarlandes in Saarbrücken, under the supervision of Prof. Theophil Eicher in a sandwich program with Facultad de Química (Uruguay). Back to Uruguay, he obtained an assistant position at Facultad de Química and he focuses his research on the synthesis of small natural molecules with potential biological activities. In 2007 he presented a patent application in collaboration with paraguayan researchers that describes the synthesis of a potent natural product against Leishmania sp. He currently teaches basic and advanced organic chemistry and he also supervises ungraduated and postgraduate research students as associate professor of the Department of Organic Chemistry at the Facultad de Química.

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