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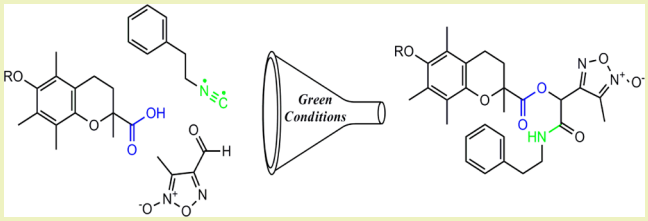
Green Conditions for Passerini Three-Component Synthesis of Tocopherol Analogues

Mariana Ingold, Gloria V. López,* and Williams Porcal*

Grupo de Química Medicinal, Laboratorio de Química Orgánica, Facultad de Ciencias-Facultad de Química, Universidad de la República, Iguá 4225, 11400 Montevideo, Uruguay

Supporting Information

ABSTRACT: A Passerini three-component reaction of a furoxan aldehyde, phenylethylisocyanide, and trolox derivatives under green conditions are reported. The Passerini reaction to obtain tocopherol mimetics can be efficiently carried out either solvent-free or in aqueous conditions under microwave irradiation, which are standards of green chemistry and characteristic of an ideal synthesis.



KEYWORDS: *Geen chemistry, Passerini reaction, Water, Microwave, Tocopherol*

INTRODUCTION

Atherosclerosis and its cardiovascular complications constitute the major cause of morbidity and mortality in developing countries.[1,2] An estimated 17.3 million people died from cardiovascular diseases (CVDs) in 2008, and it is expected that by 2030 more than 23 million people will die annually from CVDs. Epidemiological studies suggested that antioxidant supplementation might prevent the development of atherosclerotic lesions.[3] Recently, hybrid molecules combining vitamin E substructures (tocopherol analogues) and nitric oxide (·NO)-releasing moieties (furoxans and organic nitrates) have been developed, and promising results *in vitro* were obtained.[4−7] In this context, our group is interested on the development of nitric oxide-releasing tocopherol analogues with structural diversity, which is highly desirable and valuable for medicinal chemistry and drug candidate discovery. Diversity-oriented synthesis (DOS) via multicomponent reactions (MCRs) has become a powerful protocol to access bioactive molecules. MCRs are ideal for DOS because diversity can be readily introduced through each component participating in the reaction.[8,9] Other important aspects of this methodology are the characteristics of an "ideal synthesis", such as selectivity, high reaction rate, atom economy, time and energy savings, simple one-pot synthesis, and environmentally friendly conditions.[10−12] MCRs are one-pot procedures in which at least three easily accessible starting materials react to give a single reaction product, in which most of the atoms of the starting materials are incorporated.[13] A widely known multicomponent reaction is the Passerini reaction.[14−17] During this three-component reaction, a carboxylic acid, an aldehyde, and an isocyanide react to yield an α-acyloxycarboxamide, an important intermediate for chemical synthesis and drug candidates discovery. The Passerini reaction is generally performed in an organic solvent such as CH_2Cl_2 or MeOH, and long reaction times are often required. Generally, under these conditions, low yields are obtained. Recently, Pirrung and Das Sarma described a significant rate enhancement for the Passerini reaction when the organic solvent was replaced by water.[18,19] This acceleration has been attributed to factors such as the cohesive energy density of water, hydrophobic effect, and increased hydrogen bonding in the transition state; however, these phenomena have been the subject of several discussions until today.[20−22] Many of these reactions are biphasic, so water should not be seen as a traditional solvent. Water is the most abundant and environmentally friendly solvent in nature. In recent years, many efforts have been invested in the development of aqueous phase organic synthesis.[23,24] In this context, its combined use with microwave energy provides an excellent tool for achieving an accelerated, eco-friendly, and environmentally clean organic synthesis.[25−27] The use of microwave irradiation in this direction can offer many advantages such as shortened reaction times, enhanced reaction rates, and high yields. Herein, we describe the development of tocopherol analogues containing the NO-donor furoxan through a Passerini reaction under green conditions by combining water or solvent-free conditons with microwave irradiation.

EXPERIMENTAL SECTION

General Procedure. *Passerini Reaction.* To a suspension of chromancarboxylic acid (1 equiv) in water (3.3 mL/mmol), furoxan aldehyde (1 equiv) and phenylethylisocyanide (1 equiv) were added. The resulting mixture was vigorously stirred for 4−72 h at room temperature. Next, the suspension was treated with aqueous-saturated $NaHCO_3$ and extracted with EtOAc. After the work-up, the combined organic layers were dried with sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, mixtures of petroleum ether/EtOAc).

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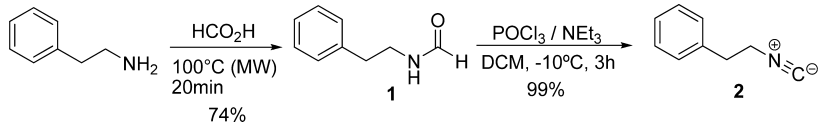
Scheme 1. Synthesis of Phenylethylisocyanide 2



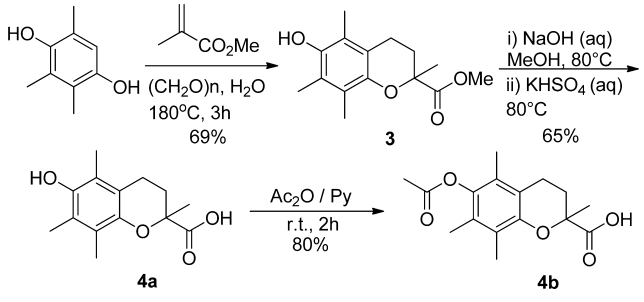
Microwave-Assisted Synthesis. A glass tube was charged sequentially with water (3.3 mL/mmol), chromancarboxylic acid (1 equiv), furoxan aldehyde (1 equiv), and phenylethylisocyanide (1 equiv). The test tube was then sealed with a Teflon septum and heated 5 min at 60 °C by microwave irradiation. The vial was cooled, and the crude reaction mixture was treated with aqueous-saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated sodium chloride solution, dried with sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, mixtures of petroleum ether/EtOAc).

RESULTS AND DISCUSSION

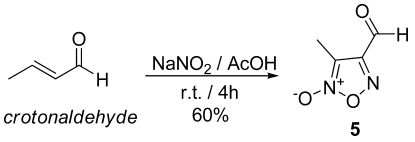
In the light of our recent research in the area of MCRs and our experience in the chemistry of tocopherol analogues containing NO-donors, we proposed a Passerini coupling of an isocyanide with furoxan aldehyde and tocopherol analogue carboxylic acid under green conditions. The isocyanide **2** was selected as a model of reactivity because its structure and physicochemical properties make it suitable to be easily synthesized in our laboratory. Thus, the phenylethylisocyanide **2** was synthesized using a synthetic route in two steps as shown in Scheme 1. First, the formation of *N*-(2-phenylethyl)formamide was carried out using phenylethylamine and formic acid as reagents. Generally, the synthesis of carboxamides from amines and carboxylic acids implies the activation of the carboxylic group. Recently, the synthesis of amides from primary amines and carboxylic acids were reported under solvent-free conditions using microwave irradiation.[28] In this sense, we performed this reaction using a multimode reactor (WX-4000 from EU Chemical Instrument Co) with accurate control of power and temperature (with an optical fiber) under mechanical stirring to avoid a macroscopic hot spot. Microwave irradiation at 100 °C for 20 min provided, after a simple extractive work-up, the desired target amide **1** in 74% isolated yield (Scheme 1). In the next step, the isocyanide **2** was obtained in excellent yield following a standard procedure that involves dehydration of formamide **1** using phosphoryl chloride and triethylamine (Scheme 1).[29]

The preparation of (*R*,*S*)-6-hydroxy-2,5,7,8-tetramethylchromancarboxylic acid **4a** (trolox) and its derivative **4b** was carried out according to the synthetic route illustrated in Scheme 2.[5,30] First, trolox methyl ester **3** was prepared and hydrolyzed to the desired carboxylic acid. Finally, **4a** was treated with acetic anhydride in the presence of pyridine to give the desired acetate derivative **4b**.[5] In the first step of this synthetic route, namely, the formation of the chroman ring, a phenol, an olefin, and formaldehyde react in a single reaction stage under mild conditions in the absence of catalyst and in the presence of water, without the use of co-solvents. Good yields were obtained when a pressure reactor was used for carrying out the reaction. These conditions are in accordance with principles of green chemistry. Simultaneously, to obtain formylfuroxan **5**, crotonaldehyde was treated with an aqueous solution of sodium nitrite overnight at room temperature to render the desired product (Scheme 3).[31] This method provides a clean synthesis of this important heterocycle.

Scheme 2. Synthesis of Trolox Derivatives under Green Conditions

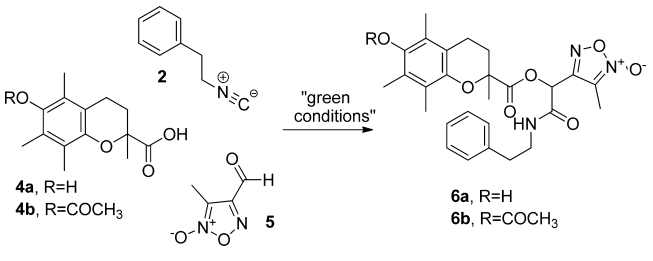


Scheme 3. Synthesis of Formylfuroxan 4



Once the key starting reagents were obtained, preliminary efforts were mainly focused on the optimization of the reaction conditions with water-insoluble organic compounds in aqueous suspension reactions "on water". Although these reactions have received a great deal of attention due to their high efficiency and simple synthetic protocols, such reactions are still rare. As a prototype, the Passerini reaction involving phenylethylisocyanide **2**, furoxan aldehyde **5** ,and tocopherol analogue carboxylic acid **4a** or **4b** (Scheme 4) was studied under various green conditions summarized in Table 1.

Scheme 4. Synthesis of α-Acyloxycarboxamides *via* Passerini Reaction



In first place, reaction conditions were studied using phenylethylisocyanide **2**, acid **4a**, and formylfuroxan **5** as starting material. Initially, we tried to obtain α-acyloxycarboxamide derivative from the vitamin E hydrosoluble analogue **4a** (trolox) in order to incorporate the tocopherol antioxidant fragment in the final product in a one-pot reaction (Scheme 5, path B). This is in agreement with green chemistry principles to avoid protecting and deprotecting phenol group steps.

Initially, the reaction was studied with CH_2Cl_2, commonly used for Passerini reactions. Product **6a** rendered a yield of 50%

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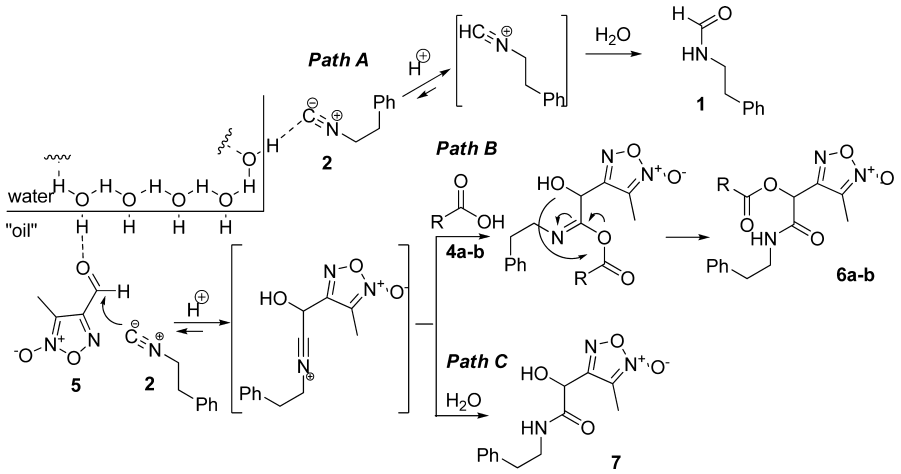
Table 1. Synthesis of α-Acyloxycarboxamides 6a−b under Green Conditions

entry	carboxylic acid	solvent	time (h)	temp (°C)	yield (%)
1	**4a**	CH_2Cl_2	4	25	50
2	**4a**	H_2O	4	25	31
3	**4a**	H_2O	24	25	33
4	**4a**	H_2O	72	25	33
5	**4a**	2.5 M aq. LiBr	4	25	45
6	**4a**	1.0 M aq. glucose	4	25	43
8	**4a**	H_2O/acetonitrile (3:1)	72	25	23
9	**4a**	H_2O/acetonitrile (1:3)	72	25	30
10	**4a**	acetonitrile	72	25	62
11	**4a**	H_2O	5 min	60 (MW)	62
12	**4a**	H_2O	5 min	60	17
13	**4a**	acetonitrile	10 min	60 (MW)	64
14	**4a**	solvent free	10 min	nd[a]	70
15	**4b**	H_2O	24	25	60
16	**4b**	H_2O	5 min	60 (MW)	42
17	**4b**	H_2O	5 min	60	30
18	**4b**	solvent free	10 min	nd[a]	45
19	benzoic acid	H_2O	24	25	64

[a]nd: not determined. Power: 100 W.

Scheme 5. Proposed Mechanism for Passerini Three-Component Synthesis of Tocopherol Analogues via on-Water Process



(Table 1, entry 1) under homogeneous conditions. When water was used, isocyanide **2** and aldehyde **5** were poorly soluble, and the Passerini product was obtained in moderate yield within 4 h (31%, Table 1, entry 2). The same yields were observed at higher reaction times (Table 1, entries 3 and 4). Under the reaction conditions mentioned above, compound **4a** did not react completely, finding formamide **2** and the hydrolyzed product **7** in the reaction mixture, as observed by TLC and ^{1}H NMR (<10%). In the past few years, several authors have described nonpolar organic reactions using water, where hydrophobic interactions seem to be responsible for the enhanced speed in which these reactions take place.[19,32] Apparently, the reaction occurs inside of a cavity where water disposes around nonpolar organic solutes in an ordered structure forming clathrates.[19] Therefore, we could attribute the moderate yield obtained here to the polar characteristic of the acid used. Some reactant could be solved by water, and the rest could be at the aqueous−organic interface available for the reaction with the other two components in the mix. This could be confirmed by the formation of amide **2** and α-hydroxycarboxamide **7** in low proportion in a Passerini alternative route (Scheme 5, paths A and C). In this aspect, when trolox acetate **4b** and benzoic acid were used, the Passerini products were obtained in 60% and 64% yields, respectively, (Table 1, entries 15 and 19). These results demonstrate the importance that the hydrophobic effects play in this reaction when it takes place in an aqueous media.

On the other hand, multicomponent reactions like Passerini have negative activation volumes; thus, they can be accelerated in high pressure conditions.[19] Generally, dissolved electrolytes increase internal pressure of water affecting activation volume ($\Delta V\#$) of a reaction in the same way that a pressure applied externally does.[23] Therefore, internal pressure of water influences the velocity of the nonpolar reaction that takes place in water the same as external pressure does. In this sense, we used high amounts of LiBr (2.5 M) in aqueous media, and we found that reaction yield improved in a short reaction time, implying the salting-out effect on the organic compounds (Table 1, entry 5). Adding co-solutes could also improve multicomponent reactions in aqueous media.[18] Addition of inorganic salts or organic co-solutes has been used to vary the reaction rates in aqueous conditions.[32] Co-solutes can interact

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with water by hydrogen bonds or dipole−dipole interactions resulting in a more organized water structure. Thus, the main effect of co-solutes such as glucose is to alter the hydrophobic interaction through water structure modification.[33] In fact, when the Passerini reaction was carried out using glucose 1 M, product **6a** was obtained in higher yield in comparison to when pure water was used (Table 1, entries 2 and 6). Also, product **6a** was obtained in low yield when a mix of acetonitrile−water was used as the solvent (Table 1, entries 8 and 9). Meanwhile, when acetonitrile was used as the solvent at room temperature, the Passerini product was obtained in better yield, but a long reaction time was needed (Table 1, entry 10).

In the last few years, the use of microwave irradiation (MW) has been popular when classic organic reactions need to be simplified or improved. This nonconventional methodology often drives to higher reaction yields, shorter reaction times, and cleaner reactions. Besides, solvent-free reactions combined with MW use result in an efficient and secure technology, which is a necessary condition in green chemistry. In this context, because MCR reactions need to be faster, MW has become the method of choice to perform these types of reactions. In fact, when Passerini coupling was carried out using MW at 60 °C, higher yields were obtained in drastically shortened times.

When the reaction was tested at higher temperatures (80 and 100 °C), hydrolysis products (Scheme 5, compounds **1** and **7**) were obtained in greater proportion (results not shown). Therefore, a temperature of 60 °C was selected to carry out the microwave experiments. When aqueous media and MW were used, the yield of product **6a** was duplicated in only 5 min. A similar yield was obtained when the reaction was carried out in acetonitrile as solvent instead of water but for 10 min (Table 1, entries 11 and 13). Even higher yields were obtained under microwave irradiation for 10 min at 100 W under solvent-free conditions (Table 1, entry 14). Furthermore, when acetate **4b** was used as starting reagent, using both aqueous and solvent-free conditions under microwave heating, amide **6b** was obtained with a similar yield in a short time (Table 1, entries 16 and 18). In addition, the desired amides **6a** and **6b** were obtained in 17% and 30% yield, respectively, under conventional heating at 60 °C (Table 1, entries 12 and 17). Thus, a substantial improvement of yields was observed when reactions were run under microwave irradiation instead of conventional heating. On the basis of the results obtained, an accelerating effect of microwave use was revealed for the Passerini multicomponent reaction according to our working conditions.

Structures of Passerini products **6a** and **6b** (Scheme 4) were deduced from their mass, IR, ^{1}H NMR, and ^{13}C NMR spectra (see Experimental Section and Supporting Information). Equimolar mixtures of diastereoisomeric products were obtained in all reactions. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z (%) values, 509 ($M^{+\cdot}$, 100) and 551 ($M^{+\cdot}$, 12) to **6a** and **6b**, respectively. The ^{1}H NMR spectrum of **6a** exhibited a characteristic signal, for example, multiplet signals for $CH_2NHC{=}O$ of the phenethyl group (3.03−3.54 and ppm), singlet signals for the methinic group (5.93 and 6.10 ppm) and phenolic OH (4.46 and 4.59 ppm), and triplet signals for the $NHC{=}O$ group (5.53 and 6.08 ppm). Characteristic ^{13}C NMR signals of **6a** were present for the two carbonyls at 164 and 172 ppm corresponding to the amide and ester group, respectively, methinic carbon at 67 ppm, and carbons of the furoxan ring at 112 and 153 ppm. The ^{1}H NMR and ^{13}C NMR of **6b** were similar to those of **6a** except for the acetyl group (Supporting Information).

In summary, hybrid molecules combining vitamin E substructures (tocopherol analogues) and nitric oxide-releasing moiety (furoxan) have been synthesized through a Passerini reaction under environmentally benign conditions (in water or solventless, with microwave irradiation) in good yields. Compared to the classical method, the advantages of the present procedure are milder conditions, shorter reaction time, cleaner reactions with improved yields, and experimental simplicity. This article highlights the importance of water-promoted diversity-oriented synthesis methodology (via multicomponent reaction) in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods, experimental procedures, characterization data for compounds, and copies of ^{1}H NMR, ^{13}C NMR, EI-MS, and HRMS. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Fax: +598 25250749. Tel.: +598 25258618/7216. E-mail: vlopez@fq.edu.uy (G.V.L.).

*Fax: +598 25250749. Tel.: +598 25258618/7216. E-mail: wporcal@fq.edu.uy (W.P.).

Notes

The authors declare no competing financial interest.

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