Review Article

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Trends in Green Chemistry
ISSN 2471-9889

2021
Vol.7 No.1:32

Development and Optimization of a Green 2-Step Stereospecific Triazol Synthesis

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Received: May 26, 2021; **Accepted:** June 09, 2021; **Published:** June 16, 2021

Citation: Guillot M, Rian O, Leyssens T (2021) Development and Optimization of a Green 2-Step Stereospecific Triazol Synthesis Trends in Green Chem 7 :1:32

Abstract

The development of green chemical processes has gained increasing importance since the introduction of the concept 21 years ago. Green alternatives are even more important when speaking of enantiopure synthesis. However, developing an efficient green process comes with obstacles, especially when one wants to carry out SN2 reactions in water. In this paper, we developed and optimized a 2-step stereospecific synthesis starting from L-Phenylalanine and yielding (R)-2-(1H-1,2,4-triazol-1-yl)-3-phenylpropanoic acid ((R)-BnTAA), involving a total of 3 SN2 reactions. The reaction was designed to minimize waste production and match other green chemistry criteria. The reaction was studied by H1NMR in order to maximize efficiency. In the end, we present a green process with a minimized waste

Key words: H1NMR; Chemical process; Green; Efficiency

Introduction

During the last 20 years, ecological awareness has become widespread. Chemists can take responsibility toward the planet by assuring developed processes are green [1]. Green chemistry revolves around twelve principles, which if all applied would lead to safe and sustainable processes [1]. Among those twelve principles, waste prevention is a main pillar when considering chemical production. Indeed, efficient chemical processes often produce a large amount of waste. The treatment of waste does not only imply important costs, but also carries an intrinsic toxicity due to the use of associated chemicals. That is why, the use of less hazardous chemicals, safer products and solvents are core principles of green chemistry [2]. Also, using renewable feedstock and developing energy-efficient processes are important concepts for the development of sustainable processes. For instance, an efficient process carried out at high temperature or at sub-zero temperatures requires a lot of energy generally produced from nonrenewable resources.

In the world of 1,2,4-triazoles, their derivatives are often studied as effective fungicides, due to the faculty of triazols to inhibit sterol 14R-demethylase, hereby disrupting the cell-wall formation of fungi [3]. Consequently, they have been subject of numerous patentsand research contributions. Their application is however not limited to this particular effect, as possible applications are also studied in the medical field for various uses from chronic renal desease, passing by bladder hyperactivity, metabolic syndrome, anxiety disorderand immunodeficiency desease to anti-cancer drugs to only cite a few.

Formation of a 1,2,4 triazol compound is either carried out by substitution of a good leaving group by a 1H-1,2,4-triazole or by forming the triazole on the compound, through condensation reactions [4]. But, despite a strong presence in the literature, those reactions lack a green development. Indeed, in the case of the substitution reactions, they are almost all carried out in organic solvents like acetonitrile, dimethylformamide, tetrahydrofuran, acetone or even ethanol. There are some occurrence of SN2 reaction in water but only on primary carbons, and most of the time, the yields are poorand/or the reaction requires the use of additives, strong heatingor long reaction times. When it comes to secondary carbons, SN2 reactions are in general slow because of steric hindrance. Furthermore, water-based SN2 reactions on secondary carbons are even less favored because water is a protic solvent and can compete with the nucleophile for substitution. That is why water has not yet been explored in this context, despite its general compatibility with the reactants. Consequently, there is a need for development of green approaches on SN2 reactions focusing on secondary carbons, even more so as they are stereospecific with alternative asymmetric synthesis rarely being green due to the use of toxic catalysts.

Therefore, in this contribution we present an optimized 2-step stereospecific triazol reaction in water, yielding the desired product with high selectivity, acceptable overall yield and excellent enantiopurity while managing to decrease waste production and develop the reaction in the greenest way possible. By showing the possibility of an efficient green SN2 reaction on a secondary carbon, we hope to lead the way into the development of many more alike reactions [5].

The Reaction and Mechanism

The developed reaction yields the compound 2-(1H-1,2,4-triazol-1-yl)-3-phenylpropanoic acid (BnTAA) which shows antifungal activity but also has application as intermediate in the synthesis of new fungicides and as ligand for metal catalysed oxidation of hydrocarbons. Alongside these applications,

enantiopure BnTAA can serve as a co-former for co-crystal formation due to its hydrogen bond donor and acceptor capacity. In addition, it can also serve as a salt former for diastereomeric resolution of chiral amines due to its carboxylic acid. Since triazol compounds are interesting synthetic building blocks, BnTAA is commercially available as a racemic compound from at least 3 different companies [6] . However, no litterature record is available for the formation of enantiopure or racemic BnTAA **(Figure 1)**.

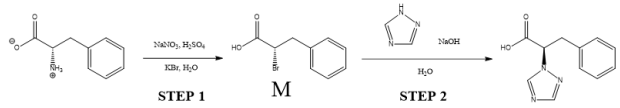

Figure 1: Schematic of a green 2-step synthesis of BnTAA.

To a stirred solution of 2 g of DL-PhenylAlanine and 5.04 g of potassium bromide in 16 mL of 2.5 M H_2SO_4 was added dropwise at 0°C 1.040 g of sodium nitrite in H_2O. Once all the sodium nitrite was added, the mixture was stirred for 1h at 0°C and then for 6h at room temperature (RT). The mixture was extracted three times with ethyl acetate. The combined organic solution was washed with brine, dried ($MgSO_4$) and concentrated in vacuum to give a crude called M 3.34 g of triazol and 1.45g of NaOH are added to 20 mL of water. The mixture is stirred at 50°C for 2 h 30. Then, the crude M is added and the mixture is stirred for 14h at 50°C. HCl (37%) is added in a dropwise manner, slowly bringing the pH down to about 2. A white product starts precipitating around pH4. The mixture is left to equilibrate overnight, filtered and washed with water. The solid is dried on vacuum and recrystallized in diethylether. 1.47 g (56%) of a white solid is obtained. This synthesis starts from an enantiopure essential amino acid, L-phenylalanine, hence from the chiral pool. This amino acid will undergo two water-based reactions, involving three SN2 reactions on its asymmetric carbon [7]. The overall result is the inversion of the stereochemistry of (S)-Phenylalanine to yield the (R)-enantiomer of the desired product with an enantiomeric excess higher than 99%. **(Figure 2)**

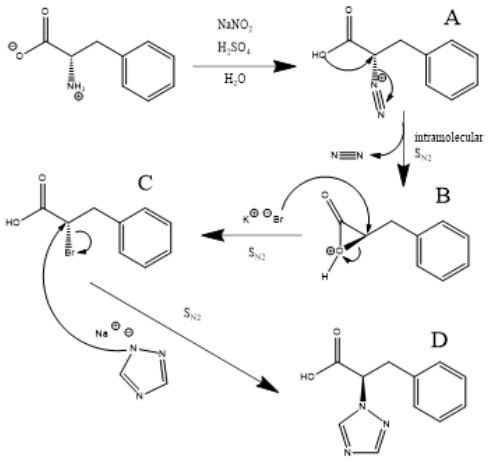

Figure 2: Mechanism of the reaction, explaining the inversion of the stereochemistry of the final product compared to the starting material.

The underlying mechanism of this reaction is assumed to involve an intramolecular SN2 of the hydroxyl of the acid on the newly formed and unstable diazonium compound (A) to yield a α-lactone (B). Then, the lactone will undergo a slower intermolecular SN2 of the nucleophile, here the bromide ion on the same carbon, opening the lactone and yielding the intermediate, (S)-2-Bromo-3-phenylpropanoic acid ((S)-BnBAA) (C). This compound undergoes again a SN2 reaction involving the deprotonated 1,2,4-triazol on the bromine, inducing a Walden inversion leading to the formation of the R enantiomer of the product, (R)-2-(1H-1,2,4-triazol-1-yl)-3-phenylpropanoic acid ((R)-BnTAA) (D). The first part of the overall reaction is already described in the literature. It derives from the Sandmeyer reaction on aryl diazonium saltsand is already considered to be environmentally friendly since its reactants and products possess relatively low hazard potential [8]. The second reaction is unpreceded in the literature, and was developed to be carried out in the greenest condition possible while yielding an efficient process.

How Is This Synthesis Green?

First, both reactions were run in water, the green solvent by definition. Moreover, the other solvents used respectively for extraction and purification are ethyl acetate and diethylether which are both recognized as generally safe (GRAS) by the FDA.

Secondly, both reactions were designed to minimize waste production **(Figure 3)**. After the first reaction, the organic phase extracted with ethyl acetate is concentrated and dried under vacuum and directly used as such.

Ethyl acetate was not considered in the waste since after concentration, it was reusable and did not need disposal.

In total, this synthesis produces two acidic aqueous waste and one non-chlorinated organic waste [9]. The production of waste for a reaction can be evaluated using the E-factor, created by Sheldon, which is calculated by dividing the mass of waste produced by the mass of product made. Consequently, the E-factor of the process was calculated.

As both reactions were run in water, the mass of solvent does not enter in the calculation of the E factor as decided by its inventor. Consequently, the E-factor of the whole process can be calculated by taking as mass of waste, the mass of the reagents that were not used to make the product of the first reaction, the quantity of solid in the aqueous waste from the second reaction and the mass of the organic waste from the recrystallization. The E-factor of this reaction is 7 which is in the fine chemicals range. The value is quite low compared to that of the synthesis of other pharmaceutical compounds, which is comprised between 25 and 100 but also in the lower part of fine chemicals whose E-factor typically reaches up to 50.

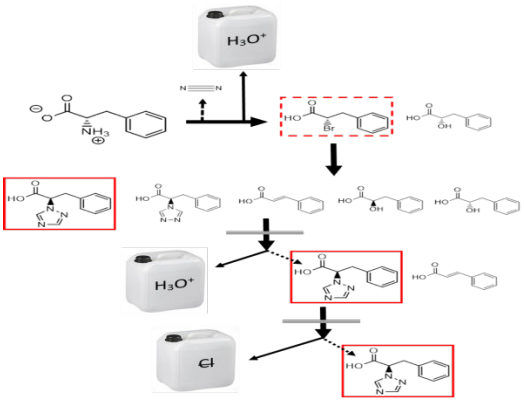

Figure 3: Schematic view of waste production for the whole process the filtration is symbolized by the grey line. The cake is given by the doted arrow.

Thirdly, the hazard of every used reagent or formed product was assessed to conclude that the reaction is globally non-hazardous. For the first reaction, the starting material is a non-toxic amino acid and it is reacted with potassium bromide, which is only irritating when put in contact with the eyes, and sulfuric acid, which is corrosive. Sodium nitrite is the only reagent, which possesses a real toxicity if ingested and can harm the environment [10]. However, it is reacted and by the end of the reaction, most of it has been transformed into nitrogen gas and water. Regarding BnBAA, it can be considered of low hazard since it completely transforms in the second reaction and its manipulation at room temperature does not require more precaution than for the other compounds. For the second reaction, 1,2,4-triazole is considered as quite safe and sodium hydroxide is only corrosive. As for the products of the reaction, the two triazolated products are fungicides and can be considered relatively safe. Cinnamic acid and phenyllactic acid can both cause skin and eye irritation but can be considered relatively safe. Regarding, the auxiliaries, 37% HCl is used to precipitate the product after the second reaction. Though corrosive and toxic for the respiratory system, its toxicity remains manageable with the use of gloves, labcoats and an aspiration unit for the fumes [11]. Finally, both reactions have a relatively low energy consumption as the first one is mostly carried out at room temperature and ambient pressure, except for the first part at 0°C, and the second one is heated at 50°C, still at ambient pressure. In addition, the product is made from renewable feedstocks (amino acids) and the product is enantiopure. No further resolution is thus needed.

Development and Optimization

Developing and optimizing an efficient process for SN2 in water is challenging. First, sodium hydroxide was chosen as a base instead of sodium or potassium carbonate to increase reactivity with the triazole (higher difference of pkA) while giving the same waste at the end. Then, HCl was preferred to sulfuric acid for the reprotonation of the acid because it would only produce table salt and water after reaction with the base. For each compound, one characteristic peak was chosen to be followed. All the characteristic peaks integrate for 1H of the molecule they refer to. From left to right, the peaks belong to cinnamic acid (1H from the double bond), BnTAA (1H from the chiral carbon), the 4-triazol by-product (1H from the chiral carbon), the starting material BnBAA (1H from the chiral carbon) and the by-product with water, 3-Phenyllacticacid (1H from the chiral carbon). Each NMR spectra was cut and the base line was smoothened for visual purposes without affecting the integrations. Each letter from the top left corner of each spectra corresponds to a certain time and temperature: a) 2h/RT, b) 1d/RT, c) 2d/RT, d) 4d/RT, e) 5d/40°C, f) 6d/50°C, g) 7d/80°C h) 8d/65°C. The next parameters to tune were the selectivity and the speed of the reaction. Indeed, SN2 reactions are always in competition with second order elimination (E2) reactions. In addition, because water was used as solvent, hydroxyl ions compete with the triazole as nucleophile. Regarding the kinetics, the rate of the reaction is slowed down due to the use of water, which is protic and decreases the reactivity of the nucleophile. Heating is not always preferred to increase yield, as selectivity will be affected considering rates of both SN2 and E2 reaction are impacted. To identify ideal reaction time and temperature, the reaction behavior was studied using H1NMR **(Figure 4)**. The results of this experiment clearly showed that no matter the time of reaction, the use of temperatures lower than 80°C did not lead to an increase in the rate of elimination, maintaining it slow compared to the others. Moreover, at room temperature the competition reaction with water as a nucleophile was almost inexistent. However, increasing the temperature the rate of this reaction increased and eventually overcame the SN2 reaction involving the triazole, as observed at 40°C. Past 50°C, the reaction with water became so fast, it was almost the only one occurring. Even though in principle one could therefore perform the entire reaction at room temperature, after 2 days, the desired substitution slowed down strongly and after two more days of reaction, the increase of product was trivial. Consequently, if a higher yield is aimed for as well as consumption of all the starting material, heating is required [12]. We chose to split the apple in two in order to have a good compromise between selectivity and reaction time, selecting a reaction temperature of 50°C.

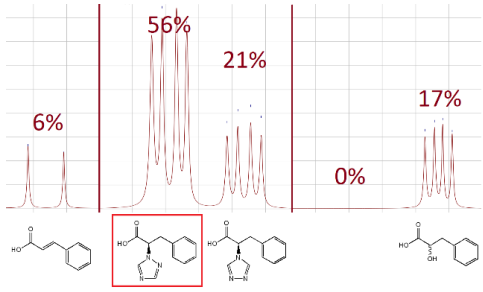

Figure 4: NMR in D2O of the mixture obtained post reaction with the optimized condition, before addition of HCl.

The characteristic peaks shown are the same as in Figure 3, with the same order. The NMR was cut and the base line smoothened for visual purposes. In order to decrease the reactivity of water, the concentration of triazole in water was increased. To increase selectivity and rate of the reaction, the quantity of base was set to 0.75 equivalent of triazol (Le Chatelier's principle). Finally, to be sure the base reacts first with the triazole, they were stirred in water for 2h30 at 50°C prior to

the addition of BnBAA. This optimized process was ran for 14 hours and the final mixture was analyzed by NMR. After 14h there is no more reactant present. Furthermore, the selectivity in the right product is higher than 50%, and if the triazole by-product is included, the selectivity of the triazole over the elimination reaction and the hydroxyl substitution is 73% for 27%, meaning at least 73% of the reagent reacted with the triazole.

Discussion and Conclusion

A 2-step green SN2 based synthesis was developed and optimized to yield an efficient and environmentally friendly process leading to the formation of an enantiopure product. The optimized process overcame two major obstacles of a secondary carbon-SN2 reaction in water: the selectivity towards the right product and the efficiency of the reaction (yield versus time). The control of the temperature and the pre-reaction of the triazole with the base were key to getting this process to work. It must be noted that this process can also be applied on the other enantiomer of phenylalanine, leading to a product of opposite chirality than the one presented here. The reaction would still remain green, even though the starting material is no longer a natural amino acid. Furthermore, the process could be applied to other α-amino acids to yield new building blocks with a 1,2,4-triazol moiety or even other types of nucleophile.

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