The Retro-Aza-Michael Reaction: How Process Optimization Led to New Scientific Insights

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La reacción Retro-Aza-Michael: cómo la optimización de procesos condujo a nuevos conocimientos científicos

La reacció Retro-Aza-Michael: com l'optimització de processos va conduir a nous coneixements científics.

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ABSTRACT

The synthesis of 2-(2-methylaminoethyl)pyridine from the reaction between 2-vinylpyridine and methylamine serves as a crucial exploration into the reversibility of the aza-Michael reaction. The results unequivocally demonstrate the notable reversibility inherent in the aza-Michael reaction. This characteristic assumes a pivotal role in fostering heightened selectivity, particularly in the realm of Flow Chemistry, where operating temperatures surpass the typical boiling points of the involved mixtures. A preliminary kinetic model, grounded in first-order reactions, aligns well with the experimental data. Results from microwave and Flow Chemistry allow for an initial approximation of the parameters governing the observed equilibrium, providing a foundational understanding of the reaction dynamics. This insight into the reversibility and kinetic aspects of the aza-Michael reaction contributes to the optimization of conditions for enhanced control and efficiency in synthetic processes, particularly under the unique conditions presented by Flow Chemistry.

Keywords: Aza-Michael addition, Microwave Reactors, Flow Chemistry, Optimization, Reversibility, Selectivity

RESUMEN

La síntesis de 2-(2-metilaminoetil)piridina a partir de la reacción entre 2-vinilpiridina y metilamina sirve como una exploración crucial de la reversibilidad de la reacción aza-Michael. Los resultados demuestran inequívocamente la notable reversibilidad inherente a la reacción de aza-Michael. Esta característica asume un papel fundamental en el fomento de una mayor selectividad, particularmente en el ámbito de la química de flujo, donde las temperaturas de funcionamiento superan los puntos de ebullición típicos de las mezclas involucradas. Un modelo cinético preliminar, basado en reacciones de primer orden, se alinea bien con los datos experimentales. Los resultados de la química de flujo y microondas permiten una aproximación inicial de los parámetros que gobiernan el equilibrio observado, proporcionando una comprensión fundamental de la dinámica de la reacción. Esta comprensión de la reversibilidad y los aspectos cinéticos de la reacción aza-Michael contribuye a la optimización de las condiciones para un mayor control y eficiencia en los procesos sintéticos, particularmente en las condiciones únicas presentadas por Flow Chemistry.

Paraules clau: Adición de Aza-Michael, Reactores de Microondas, Química de Flujo, Optimización, Reversibilidad, Selectividad

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RESUM

La síntesi de 2-(2-metilaminoetil)piridina a partir de la reacció entre la 2-vinilpiridina i la metilamina serveix com a exploració crucial de la reversibilitat de la reacció aza-Michael. Els resultats demostren inequívocament la notable reversibilitat inherent a la reacció aza-Michael. Aquesta característica assumeix un paper fonamental a l'hora de fomentar una selectivitat elevada, especialment en l'àmbit de la química de flux, on les temperatures de funcionament superen els punts d'ebullició típics de les mescles implicades. Un model cinètic preliminar, basat en reaccions de primer ordre, s'alinea bé amb les dades experimentals. Els resultats de la química de microones i de flux permeten una aproximació inicial dels paràmetres que regeixen l'equilibri observat, proporcionant una comprensió fonamental de la dinàmica de la reacció. Aquesta visió de la reversibilitat i els aspectes cinètics de la reacció aza-Michael contribueix a l'optimització de les condicions per millorar el control i l'eficiència en els processos sintètics, especialment en les condicions úniques presentades per Flow Chemistry.

Paraules clau: Addició d'Aza-Michael, reactors de microones, química de flux, optimització, reversibilitat, selectivitat

INTRODUCTION

A deep understanding of a reaction's mechanism often facilitates the development of more efficient industrial processes. Surprisingly, in the case of the aza-Michael reaction, it was the optimization of the industrial process and the adoption of Flow Chemistry that not only enhanced productivity and selectivity but also contributed to a more comprehensive understanding of the reaction's mechanism.

Michael additions and other Michael-type reactions[1] are perhaps some of the most used reactions in organic synthesis to create C-C bonds. Additionally, heteroatom nucleophiles add to conjugated systems to produce Michael-type products. The addition of aniline to conjugated aldehydes[2] or the addition of amines to conjugated esters [3,4,5,6,7,8] are typical examples of aza-Michael-type reactions. Various primary and secondary amines have been demonstrated to undergo Michael addition reactions with alkenyl-substituted N-heterocycles [9,10,11,12,13,14]. Charmot et. al.[15] during the preparation of 3-vinyl pyridines to be used as monomers, indirectly confirmed how the position of the alkenyl group has a special relevance (Figure 1). In 2017, Kennedy and Klump[16] studied the addition of esters of amino acids to alkenyl N-heterocycles. An example is the addition of valine methyl ester to 2-vinyl pyridine used in that work to check out possible catalysts. These authors observed that NMR experiments suggest that the addition reaction would be reversible under acidic conditions, but they did not do any more investigation in this sense.

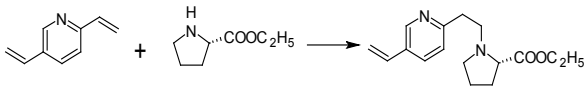


Figure 1. *Synthesis of 3-vinyl pyridine derivatives to be used as monomers[15].*

The simplest model of this type of reaction is perhaps the synthesis of 2-(2-methylaminoethyl)pyridine, involving just the addition of methylamine to 2-vinylpyridine (Figure 2).

Since its commercial synthesis was patented in 1965[17], the industrial experience demonstrates that it has a high conversion based on 2-vinylpyridine but has a poor selectivity of about 60-70%[18]. The main by-product is the product of double addition (Figure 2), N-methyl-2-(pyridin-2-yl)-N-(2-(pyridin-2-yl)ethyl)ethanamine. Consequently, the industrial synthesis of 2-(2-methylaminoethyl)pyridine is carried out with a significant excess of methylamine and long dosing times trying to avoid as far as possible the formation of the product of double addition. Furthermore, the reaction is carried out in an aqueous medium but usually includes a co-solvent trying to facilitate mass transfer and increase the reaction rate. The extra costs are then not just economical but environmental.

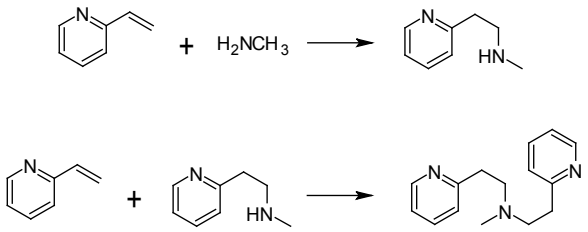


Figure 2. *Synthesis of 2-(2-methylaminoethyl)pyridine and formation of the product of double addition.*

However, Yan *et al.* in 2020[19] claimed that by carrying out this reaction in a flow reactor under pressure and at high temperatures, both the reaction rate and the selectivity are substantially improved. Sun *et al.*[20] recently published a paper confirming the claims of Yan *et al.* and demonstrating that the use of co-solvents is not necessary at all.

The objective of this paper is to use the synthesis of 2-(2-methylaminoethyl)pyridine as a model to explore if the potential reversibility of the aza-Michael reaction suggested by Kennedy and Klump[16] contributes to the increase of selectivity claimed by Yan et al.[19] and Sun et al.[20].

MATERIALS AND METHODS

Methylamine (40% w/w solution in water), 2-vinylpyridine, 2-(2-Methylaminoethyl)pyridine, N-methyl-2-(pyridin-2-yl)-N-(2-(pyridin-2-yl)ethyl)ethanamine, sodium dodecyl sulfate, sulfuric acid 98% for HPLC,

water for UHPLC and tetrabutylammonium hydrogen sulfate were supplied by Merck. Hydrochloric acid and Sodium Hydroxide were supplied by Panreac Applichem and Acetonitrile, by Fisher Scientific.

The microwave reactor employed for the experiment was a Biotage® Initiator Classic, complemented by Biotage® microwave reaction vials ranging in capacity from 10 to 20 mL. The flow chemistry system consisted of a Syrris Asia, comprising a pressurized input store, a double-channel syringe pump (pumps 1 and 2), a two-way 5 mL reagent injector (loops 1 and 2), a chip climate controller, a 1000 µL Asia microreactor with 2 inputs, and an Asia pressure controller. The high-performance liquid chromatography (HPLC) system utilized in the analysis was an Agilent Technologies 1200 Series S-49, equipped with an Agilent Zorbax Eclipse XDB-C18 column measuring 150x3 mm.

METHYLAMINE SOLUTION

In a three-necked round-bottomed flask equipped with magnetic stirring, a dosing funnel, a thermometer, and a pH meter, and placed in an ice-water bath, the desired amount of solution of methylamine in water is carefully introduced. Hydrochloric acid is cautiously dispensed from the dosing funnel to achieve the designated pH. Throughout the process, the temperature must be maintained below 30ºC.

BATCH REACTIONS

In a three-necked round-bottomed flask, fitted with mechanical stirring, a dosing funnel, and a thermometer, the designated quantity of a methylamine solution is introduced. The system is then heated to reflux, and the necessary amount of 2-vinylpyridine is rapidly introduced. Samples are collected at various time points during the process and promptly cooled for further analysis.

MICROWAVE REACTIONS

9 mL of amine solution (pH 8.2) and 4 mL of 2-vinylpyridine are carefully introduced in a microwave reaction vial. A magnetic stirring piece is introduced and the vial is sealed. The desired temperature and time of reaction are programmed, and the vial is introduced into the system. After cooling, the result is analysed.

FLOW REACTIONS

Initially, the injection involves pure water. Following this, Loop 1 is charged with 2-vinylpyridine, while Loop 2 is filled with the previously prepared solution of methylamine (pH 8.2). Pump 1 operates at a flow rate of 80 µL/min, and Pump 2 at 170 mL/min, resulting in a residence time of 4 minutes and a molar ratio of amine to 2-vinylpyridine of 1.45. The reactor temperature is set at 150ºC. Once the system reaches a stabilized state, both loops are simultaneously engaged to inject their contents into the reactor. After nearly three times the residence time has elapsed, a sample of the product is collected for subsequent analysis.

ANALYSIS

The mobile phase is meticulously formulated by combining 15 mL of a 10% v/v solution of sulfuric acid in water with 35 mL of a solution containing 1.7 g of tetrabutylammonium hydrogen sulfate dissolved in 100 mL of water. To this solution, 2.0 g of sodium dodecyl sulfate are added, followed by the incorporation of 650 mL of water. The pH is precisely adjusted to 3.3 using a sodium hydroxide solution. The resulting mixture undergoes filtration through a 200 nm membrane, and subsequently, 330 mL of acetonitrile are introduced to complete the formulation.

Chromatographic conditions were: temperature 20ºC, flow 1 mL/min, sample size 20 mL, record time 15 min.

Reference solutions were prepared in the range from $5{\cdot}10^{-5}$ to $2{\cdot}10^{-4}$ mol/K for three distincts compounds: 2-vinylpyridine, 2-(2-Methylaminoethyl)pyridine, and N-methyl-2-(pyridin-2-yl)-N-(2-(pyridin-2-yl)ethyl) ethanamine. These solutions were formulated in water to ensure accuracy and consistency in the experimental conditions. The retention times for the analyzed compounds are as follows: 2-vinylpyridine exhibits a retention time range of 1.37-1.38 minutes, 2-(2-Methylaminoethyl)pyridine demonstrates a range of 1.59-1.63 minutes, and N-methyl-2-(pyridin-2-yl)-N-(2-(pyridin-2-yl)ethyl)ethanamine has a retention time range of 2.68-2.71 minutes.

RESULTS AND DISCUSSION

The first step was reproducing the traditional batch procedure to obtain 2-(2-methylaminoethyl)pyridine. Figure 3 shows two identical processes carried out one including 2-propanol as a co-solvent, and the other using water as a unique solvent. Because such reactions were done at reflux, the rate differences can be attributed to the lower boiling point produced by the presence of 2-propanol. However, the shape of the green curve in Figure 3, which corresponds to the selectivity of the process carried out without IPA, gives a first clue about the reversibility of the reactions involved in the process. Initially, the selectivity decreases sharply, indicating a fast formation of the product of double addition. After some time, the selectivity grows, suggesting that the product of double addition is transformed into the desired 2-(2-methylaminoethyl)pyridine.

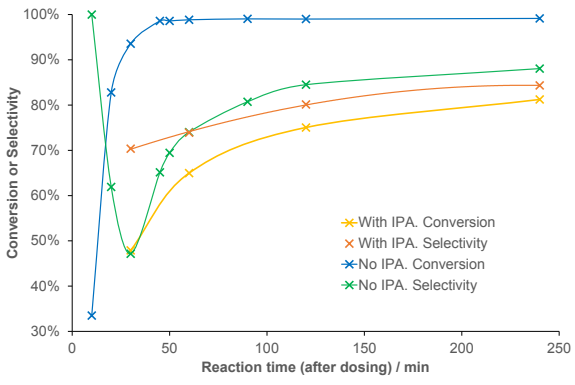


Figure 3. *Traditional batch procedure comparing the results obtained using or not 2-propanol as co-solvent.*

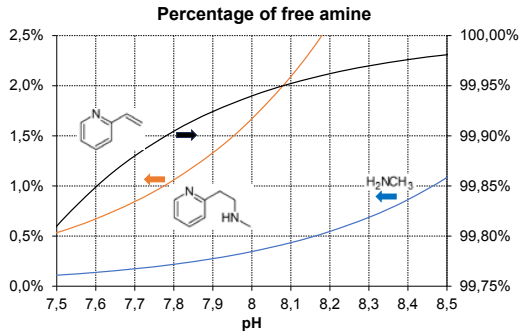


Figure 4. *Percentage of free amines at different pH.*

2-vinylpyridine is the electrophilic compound of this Michael-type reaction and methylamine is the nucleophilic one. So, the reaction would be favoured if the 2-vinyl pyridine was protonated, and the methylamine acted as a free base. However, the relative basicity of both raw materials favours the protonation of the methylamine instead of that of the 2-vinylpyridine. It could be inferred that there should be a narrow window of pH in which the reaction can progress. Figure 4 shows the result of an estimation of the percentage of free amine in solutions at different pH. The values of pKa of the conjugated bases used are 4.98 for 2-vinyl pyridine[21] 10.66 for methylamine[22] and 9.77 for 2-(2-methylaminoethyl) pyridine[23]. It appears that there is a pH range centred around 8 where there is a possibility for the coexistence of low concentrations of the cation of 2-vinyl pyridine and free methylamine. Due to the increased basicity of 2-(2-methylamino ethyl)pyridine, this compound tends to be more protonated compared to methylamine. Consequently, the formation of the double addition product would be expected to be less favourable.

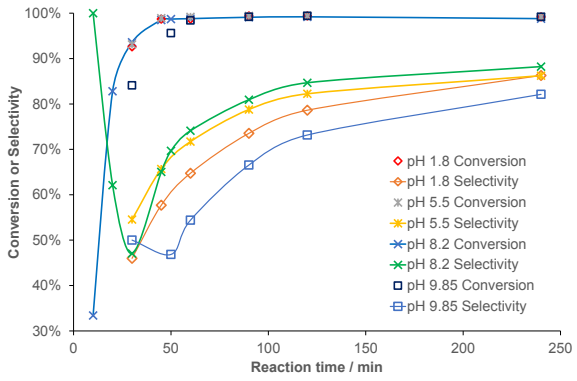
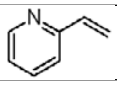
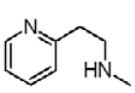
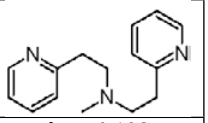


Figure 5. *Conversion and selectivity at different pH.*

However, a screening of the behaviour of the process at different initial pH (Figure 5) shows that this variable has no essential influence in the final conversion. Though, both the reaction rate and selectivity change. As expected, the best results are obtained at a pH of around 8. In all cases, the raw material 2-vinylpyridine is very fast consumed at the very beginning of the reaction. Selectivity falls, indicating the quick transformation of betahistine in the product of double addition. Finally, this one reverts progressively to 2-(2-methylaminoethyl) pyridine. The reversibility of the reaction is evident. In classical terms, it can be suggested that the formation of the product of double addition is by kinetics, but then 2-(2-methylaminoethyl)pyridine is favoured by thermodynamics.

A thorough simulation was executed by integrating the equations specified in Table 1, resulting in the illustrated outcomes in Figure 6. The reference reaction was conducted at atmospheric pressure and under reflux of water conditions at a pH of 8.2. Although the acquired results exhibit a satisfactory level of accuracy, continuous experimental efforts are in progress to fine-tune the model and attain an improved fit.

Table 1. *Simulation data*

A:		**B:**	H_2NCH_3
C:		**D:**	
$A + B \rightarrow C$ $A + C \rightarrow D$ $D \rightarrow A + C$		$r_1 = k_1 \cdot c_A \cdot c_B$ $r_2 = k_2 \cdot c_A \cdot c_C$ $r_3 = k_3 \cdot c_D$	$k_1 = 0.198$ $k_2 = 96.8$ $k_3 = 4.78$

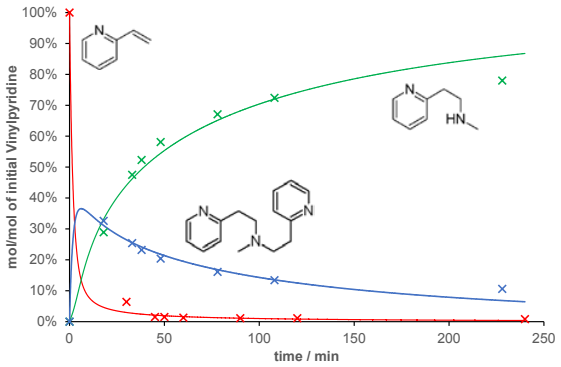


Figure 6. *Simulation results. Crosses represent experimental data and solid lines indicate simulation results.*

In addition, a quite pure sample of the product of double addition was put in the reaction conditions. The result was the formation of the desired 2-(2-methylaminoethyl) pyridine in a good yield (Figure 7). The reversibility of the aza-Michael reaction is confirmed again.

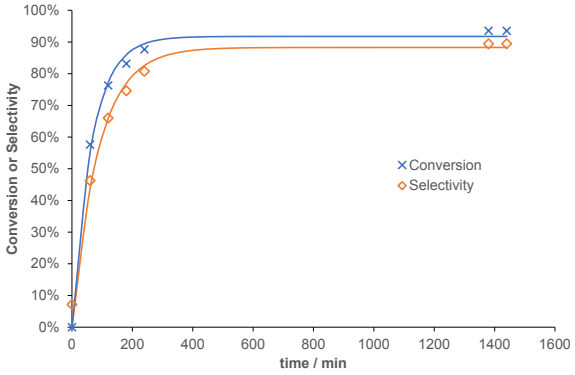


Figure 7. *Transformation of the product of double addition into 2-(2-methylaminoethyl)pyridine.*

A battery of experiments to check out the influence of the temperature in the process was performed using a microwave oven. Figure 8 shows the results of those experiments. The reaction time was adjusted according to the thumb rule that states that for a "normal" chemical reaction, the reaction rate is doubled when the temperature is increased by 10ºC. The obtained conversion curve is quite linear containing a very small change in conversion, suggesting that the reaction of consumption of the raw material follows the suggested thumb rule. However, a step in the selectivity curve is observed between 145 and 155ºC, confirming that this reaction follows a more sophisticated mechanism. It can be said that for reaction times shorter than 5 minutes and despite the increase in temperature, there is no time enough to complete the transformation of the product of double addition into 2-(2-methylaminoethyl)pyridine.

Table 2. *Experimental results at different temperatures. t_R: reaction time.*

Experiment	t_R (min)	T (°C)	p (bar)	Conversion	Selectivity	K_{eq}
1	40	115	3	98,9%	92,6%	2,03
2	20	125	5	98,1%	92,5%	1,47
3	10	135	6	98,0%	91,8%	1,51
4	5	145	7	96,9%	92,2%	1,02
5	3	155	8	96,6%	91,2%	1,05
6	1,6	165	9	96,3%	91,2%	0,964

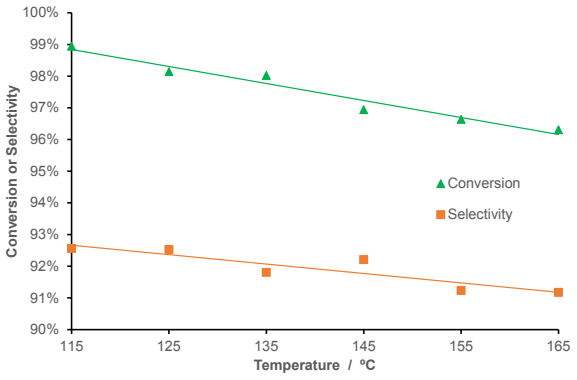


Figure 8. *Experimental results at different temperatures.*

The fitting of the van't Hoff equation to the data presented in Table 2 and Figure 8 is feasible. A preliminary estimation of the equilibrium parameters is obtained: $\Delta H^0 = -29 \pm 6\ kJ/mol$ and $\Delta S^0 = -59 \pm 14\ J/(mol \cdot K)$. Ongoing experiments are being conducted to refine the fitting and enhance the precision of these parameters.

CONCLUSIONS

The results derived from the synthesis of 2-(2-methylaminoethyl)pyridine unmistakably showcase the reversibility of the aza-Michael reaction. This reversibility stands out as a pivotal factor contributing to the enhanced selectivity in Flow Chemistry at temperatures higher than those of the normal boiling point of the mixtures.

In the initial stages of the reaction, the rapid formation of N-methyl-2-(pyridin-2-yl)-N-(2-(pyridin-2-yl)ethyl) ethanamine, resulting from double addition, efficiently depletes nearly all of the available 2-vinylpyridine. Subsequently, the product of double addition undergoes a transformation, ultimately leading to the desired 2-(2-methylaminoethyl)pyridine as the reaction progresses towards a final equilibrium. Notably, the reaction rate benefits from elevated temperatures achievable in Flow Chemistry. However, it is important to acknowledge that these higher temperatures, while promoting the reaction kinetics, also diminish the overall conversion to the desired 2-(2-methylaminoethyl)pyridine.

An initial approximate determination of the kinetic constants under water reflux, as well as the enthalpic and entropic parameters governing the equilibrium reaction, has been conducted within the temperature range of 115 to 165ºC. It is important to note that these estimations serve as preliminary values, and ongoing experimental efforts are underway to refine and enhance the accuracy of these results. Further experimental work is being undertaken with the objective of providing a more comprehensive understanding of the reaction dynamics within this temperature spectrum.

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