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Factorial study to assess an ultrasonic methodology for the allylation of 4-chloroaniline

DOI 10.1515/gps-2016-0122
Received July 13, 2016; accepted August 17, 2016; previously published online September 21, 2016

Abstract: *N*-allylanilines are important compounds that are used to access several bioactive compounds containing indole and dihydroindole nucleus. However, their preparation through allylation can lead to the undesirable *N*,*N*-diallyl byproduct. In this work, the *N*-allylation of 4-chloroaniline was studied. In order to accelerate the process and maximize the monoallylated:diallylated ratio, we reported two full factorial studies to transpose the conventional synthetic procedure to an ultrasound (US) methodology. The evaluated factors were temperature, quantity of reagents (allyl bromide and K_2CO_3), reaction time, and methodology (conventional or US). The results showed that US did not change the monoallylated:diallylated ratio, but significantly improved the reaction rate, giving increased average monoallylated and total yields of 11.4% and 18.1%, respectively ($p < 0.05$). The proposed US methodology gave the same yields and product ratio in a 4-h reaction time than the conventional 24-h procedure, without heating and using only an inexpensive US bath to conduct the reactions.

Keywords: factorial design; N-allyl-4-chloroaniline; N-allylation; ultrasonic bath; ultrasound-assisted synthesis.

1 Introduction

Substituted *N*-allylanilines are important building blocks that are used access a diverse range of organic compounds [1–5]. In particular, *N*-allylanilines can be a useful starting compound to obtain the corresponding 2-allylaniline through *aza*-Claisen rearrangement, which have been used by our group to prepare indole and dihydroindole containing molecules for medicinal chemistry purposes [1–3, 6]. In a previous work [7], we reported the optimization of an ultrasonic-based methodology to prepare the allyl 1-naphthyl ether with high yields in just 1 h of reaction in an inexpensive ultrasonic bath without additional heating. However, in the allylation of anilines, there exists the additional problem of diallylation, which leads to the undesirable *N*,*N*-diallylaniline byproduct. This byproduct makes the following steps on the preparation of the final heterocycles much more complicated, because it can also be rearranged as well as cyclized. Considering this, the synthesis of *N*-allylaniline must be optimized to obtain the maximum desired monoallylated compound and avoid the diallylated product, while generating the maximum yield.

Several reports on the preparation of *N*-allyl-4-chloroaniline have been published in the literature. In these studies, allyl bromide is the most employed allylating agent, and carbonates are the most frequent base [1–5, 8–10]. The yields reported for these reactions were usually good to excellent; however conventional methodologies were always used, and were mainly conducted under heating for several hours. Additional procedures were also published, employing allyl alcohol [11, 12], allyl carbonate [13], and other unusual allylating agents, such as allylsilanes and allyl tosilates [14, 15]. *N*,*N*-diallyl-4-chloroaniline is frequently produced in these reactions, excluding some methods that use expensive or unusual reagents/catalysts [11, 16, 17]. To the best of our knowledge, no ultrasonic methodologies have been reported for this preparation.

The ultrasound (US) energy is well known by accelerating chemical reactions [18]. This effect usually takes place through the cavitation phenomenon, that is, the formation, growth, and collapse of micrometrical bubbles formed by the propagation of a pressure wave through a liquid. The collapses generate high temperatures and pressures in the small environment within nanoseconds. However, the process can sometimes be influenced by the simple mass transfer of US waves (sometimes called false sonochemistry). On the one hand, this phenomenon can be used to speed up chemical reactions; save on time, energy, and costs; and achieve an optimized benefit-cost relation. On the other hand, this energetic process can lead to both desirable and undesirable chemical reactions

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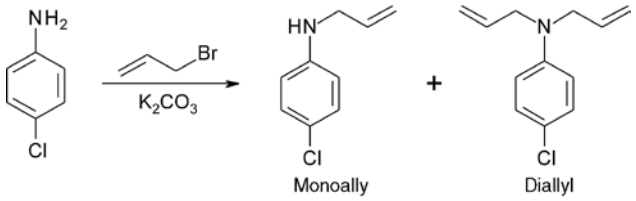

Figure 1: Scheme of synthesis of *N*-allyl-4-chloroaniline and the byproduct *N*,*N*-diallyl-4-chloroaniline.

[18]. Therefore, the results obtained with US-assisted reactions may differ from those obtained in the same conditions with conventional synthesis [19].

In this paper, we aimed to synthesize the *N*-allyl-4-chloroaniline (Figure 1) with the maximum possible yield, while avoiding or even minimizing the synthesis of the diallylated byproduct. For this purpose, we proposed several factorial designs to assess this objective in an US-assisted methodology. In addition, the assessment of a methodology to prepare this compound more rapidly using an inexpensive ultrasonic bath should be considered to make the process more convenient and "green."

2 Materials and methods

2.1 Reagents and equipment

Here, 4-Chloroaniline, allyl bromide and silica gel 70–230 mesh were obtained from Sigma-Aldrich Co. (Saint Louis, MO, USA). Potassium carbonate and other common chemicals were purchased from LabSynt Co. (Diadema, Brazil). All the chemicals were obtained in adequate purity, and no treatment was done prior to use. Ultrasonic irradiation was performed in a Ecosonics Q1.8/40A (Indaiatuba, Brazil) ultrasonic thermostated water bath (40 KHz – 55 W – 60°C). Next, ^{1}H and ^{13}C-NMR spectra were recorded in a Bruker Ultrashield 300 spectrometer, operating at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as solvent with TMS as internal standard. Chemical shifts are reported in parts per million (ppm, δ units). Coupling constants are reported in units of hertz (Hz), if applicable. Gas chromatography coupled to mass spectrometer (GC-MS) analysis were performed in a Shimadzu GC-2010 coupled to mass spectrometer GCMS-QP2010 plus, using helium as carrier gas in a silica capillary column. The low-resolution mass spectra (LRMS) were obtained through electron impact ionization (70 eV). The ion-radical and its fragments are reported in mass/charge ratio (m/*z*).

2.2 Synthetic procedure

4-Chloroaniline (5 mmol) was added with 10 ml of acetone in a flat-bottom flask. After dissolution under manual agitation, the adequate amounts of allyl bromide and K_2CO_3 (7.5 or 10.0 mmol each) were added, and the mixture was reacted by the times presented in Tables 1 and 2, under conventional magnetic stirring or in the ultrasonic bath. The solvent was evaporated, and the residue was taken-up in 15 ml of a mixture of hexane:ethyl acetate (9:1) and washed twice with brine. Afterwards, the organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude oil was analyzed through gas chromatography coupled to mass spectrometer to determine the percentage of starting material and products. *N*-Allyl-4-chloroaniline: light brown oil; ^{1}H NMR: δ = 3.73 (2H, d, *J* = 5.3 Hz, NHC<u>H</u>$_2$), 3.79 (1H, br s, NH), 5.17 (1H, dd, *J* = 10.3, 1.3 Hz, =C<u>H</u>$_2$), 5.26 (1H, dd, *J* = 17.1, 1.5 Hz, =C<u>H</u>$_2$), 5.84–5.99 (1H, m, -CH=), 6.49–6.56 (2H, m, C<u>H</u>CNH), 7.07-7.15 (2H, m, C<u>H</u>CCl); ^{13}C NMR: δ = 46.6, 114.0, 116.5, 122.0, 129.0, 135.0, 146.6; LRMS: m/*z* (rel. int.) = 167 $[M]^+$ (85), 140 (100). *N*-Diallyl-4-chloroaniline: light purple oil; ^{1}H NMR: δ = 3.84–3.93 (2H, m), 5.09–5.15 (2H, m), 5.17 (1H, s), 5.74–5.90 (1H, m), 6.55–6.63 (2H, m), 7.07–7.16 (2H, m); ^{13}C NMR: δ = 52.9, 113.5, 116.2, 121.0, 128.8, 133.5, 147.3; LRMS: m/*z* (rel. int.) = 207 $[M]^+$ (99), 180 (100), 41 (75).

2.3 Factorial study

Full factorial designs are widely employed techniques to preliminary evaluate the conditions (factors) that determine a desired response in a chemical reaction or other processes in laboratorial or industrial scale. Several examples of this approach can be found in the literature [20–23]. These preliminary results are valuable in determining the effects of these factors, especially in categorical (non-numerical) factors, such as the methodologies evaluated (conventional or US) in this work.

Table 1: Background experiments under conventional conditions in 24-h reaction.

Allyl bromide (mmol)	K_2CO_3 (mmol)	Temperature (°C)	Monoallyl yield (%)	Total yield (%)	Monoallyl ratio (%)
7.5	7.5	25	52 ± 1.9	69 ± 0.1	76 ± 2.9
7.5	7.5	60	40 ± 3.4	94 ± 1.3	43 ± 3.1
10.0	10.0	25	55 ± 5.1	76 ± 3.9	72 ± 2.9
10.0	10.0	60	36 ± 0.4	98 ± 1.1	37 ± 0.8

Table 2: Experimental conditions to evaluate the methodology, time reaction, and quantity of reagents.

Methodology	Time (h)	Reagents (mmol)	Monoallyl yield (%)	Total yield (%)	Monoallyl ratio (%)
Conventional	1.5	7.5	14 ± 0.5	14 ± 0.5	100 ± 0.0
Conventional	1.5	10.0	28 ± 0.2	28 ± 0.2	100 ± 0.0
Conventional	4.0	7.5	32 ± 0.7	35 ± 0.7	91 ± 0.2
Conventional	4.0	10.0	38 ± 1.4	45 ± 2.8	85 ± 2.2
US	1.5	7.5	28 ± 0.5	29 ± 0.5	96 ± 0.1
US	1.5	10.0	39 ± 2.5	43 ± 3.0	90 ± 0.4
US	4.0	7.5	45 ± 0.3	61 ± 0.5	74 ± 0.6
US	4.0	10.0	45 ± 0.1	61 ± 1.0	74 ± 1.2

To verify these effects in the US-based methodology, background experiments under the conventional approach were done, as well as experiments that compared both methodologies using the same conditions. *N*-allyl-4-chloroaniline (monoallyl) yield, total (monoallyl + diallyl) yield and monoallyl ratio [calculated as (monoallyl yield/total yield)x100] were selected as the studied responses. In this work, the factors (methodology, time, amount of allyl bromide and temperature) were coded in categorical levels for the design, being (−) for the low levels and + for the high levels. The experimental (uncoded) and the coded values are shown in Table 2. The effects were calculated from Eq. (1):

$$\text{Effects} = Y_{+} - Y_{-}, \quad (1)$$

where Y_{+} and Y_{-} are the means of yields obtained with high and low levels, respectively. The symbols (+) and (−) are standard notations in factorial design and their definitions do not affect the interpretation of results.

2.4 Statistical analysis

Statistical analysis was carried out using the electronic sheets available from Teófilo and Ferreira [24], and graphics were built using the Excel 2010 (version 14.0, Microsoft, Inc.) software. Estimated effects were calculated using the t-Student test, obtaining the t- and p-values to each effect. The t-value measures the magnitude of the factor effect on the response, whereas p-value measures the significance probability of a given effect. In this work, the lowest confidence level used was 95%, indicating that the measured effects were considered significant when $p < 0.05$ [24].

3 Results and discussion

The most used method to the *N*-allylation of anilines is the reaction of allyl bromide and base catalysis. Allyl bromide is a suitable reagent for nucleophilic substitution due the quality of bromine as leaving-group and the stability of allylic cation when the bromide anion leaves [7]. This stability is attributed to the stabilization of the sp^2 state by the delocalization of allylic π-bond [25]. In this reaction, a base is always used to increase the nucleophilicity of the aniline as well as to quench the HBr produced. It is usually accepted that this reaction occurs through both S_N1 and S_N2 in conventional procedures, and US may influence the mechanism involved [7].

The preparation of *N*-allyl-4-chloroaniline is usually done using DMF as solvent as well as allyl bromide and carbonates as reactants. Ramachary and Narayama [2] reported its synthesis with 70% yield after 24 h of reaction, using 1.1 equivalent of allyl bromide to avoid diallylation. In a similar fashion, Nicolaou et al. [1] reported the preparation of this compound in 12 h of reaction at room temperature, yielding only 29% of the product. Using a water-ethanol mixture as solvent, Du et al. [8] reported yields of 77% for diallylated product and only 10% of monoallyl aniline in 3.5 h of reaction at 70°C. When no base was employed, the monoallylated product was mainly obtained, but with low yield (32%).

Given that controlling the diallylation reaction is difficult, several reports that attempted to circumvent this issue can be found in the literature. Yang et al. [11] reported a method for selective preparation of monoallyl anilines using palladium-catalyzed allylation with allylic alcohol. However, the yields and product distribution depends on the alcohol amount. By allylating an *N*-protected aniline with formyl or other protecting groups, it is now possible to obtain the monoallylated product without diallylation [17]. However, at least three steps (protection-allylation-deprotection) are necessary, and in some cases strong bases, such as NaH must be used. Ultrasonic approaches were not found in our data collection conducted in the main databases.

Considering that a US-assisted methodology to access the allylation of anilines could change the distribution of the monoallylated and diallylated products, in addition to speeding up the whole process, we decided to transpose the conventional methodology to the US. Background experiments were done prior to US method to evaluate which factors would affect the yields and diallylation rate in conventional synthetic procedures. Thus, a 2^2 full factorial study was performed to verify the influence of allyl bromide quantity (1.5 equivalents and 2.0 equivalents) in the reaction and the temperatures (25°C and 60°C). The results presented in Tables 1 and 3 show that that quantity of allyl bromide (and K_2CO_3) did not have an important influence on the yields (total and monoallyl) and neither in the monoallyl ratio ($p > 0.05$). Meanwhile, temperature affected the results in a significant manner. As can be seen in Table 1, when the temperature was raised to 60°C, the yields of monoallylated product decreased around 15.7%, and the monoallyl ratio was lowered by 34.6%. However, the total yield was increased by 23.4%. This observation indicates that the higher the temperature, the greater the likelihood that a diallylated product is generated, especially when more allyl bromide is used in the reaction. Interestingly, when a higher temperature was employed, the conversion of the starting material 4-chloroaniline was almost quantitative, and the ratio of diallylated product was over 50%. Considering the fact that diallylation is an undesired effect in the context of this work, the reactions should be done in lower temperature (i.e. 25°C). As result, the runs applied in the transposition to the US methodology were all done in this temperature, thus avoiding heating during the process and saving energy.

Table 3: Calculated effects for each factor in the background experiments.

	Estimated effects	Standard-error	t	p-Value
Effects for monoallyl yield				
Global mean	45.8	±1.6	28.66	9×10^{-6}
Main effects				
Reagents	−0.5	±3.2	0.17	0.876
Temperature	−15.7	±3.2	4.92	0.008
Interaction effect				
Reagents × Temperature	−3.5	±3.2	1.10	0.334
Effects for total yield				
Global mean	84.1	±1.06	79.29	2×10^{-7}
Main effects				
Reagents	5.9	±2.12	2.79	0.050
Temperature	23.4	±2.12	11.05	4×10^{-4}
Interaction effect				
Reagents × Temperature	−1.4	±2.12	0.67	0.540
Effects for monoallyl ratio				
Global mean	57.0	±1.30	43.97	2×10^{-6}
Main effects				
Reagents	−4.8	±2.60	1.85	0.138
Temperature	−34.6	±2.60	13.34	0.002
Interaction effect				
Reagents × Temperature	−1.2	±2.60	0.48	0.658

Table 4: Calculated effects for each factor in the transposition to US methodology.

	Estimated effects	Standard-error	t	p-Value
Effects for monoallyl yield				
Global mean	33.3	±0.4	92.78	2×10^{-13}
Main effects				
Methodology	11.4	±0.7	15.84	3×10^{-7}
Time	13.1	±0.7	18.28	8×10^{-8}
Reagents	7.9	±0.7	10.96	4×10^{-6}
Interaction effect				
Methodology × Time	−1.1	±0.7	1.57	0.156
Methodology × Reagents	−2.4	±0.7	3.31	0.011
Time × Reagents	−4.6	±0.7	6.44	2×10^{-4}
Effects for total yield				
Global mean	39.2	±0.5	80.28	6×10^{-13}
Main effects				
Methodology	18.1	±1.0	18.57	7×10^{-8}
Time	22.1	±1.0	22.66	2×10^{-8}
Reagents	9.9	±1.0	10.11	8×10^{-6}
Interaction effect				
Methodology × Time	2.9	±1.0	2.94	0.019
Methodology × Reagents	−2.4	±1.0	2.43	0.041
Time × Reagents	−4.4	±1.0	4.48	0.028
Effects for monoallyl ratio				
Global mean	88.8	±0.3	355.00	4×10^{-18}
Main effects				
Methodology	−10.3	±0.5	20.50	3×10^{-8}
Time	−15.5	±0.5	31.00	1×10^{-9}
Reagents	−3.5	±0.5	7.00	1×10^{-4}
Interaction effect				
Methodology × Time	−3.5	±0.5	6.50	2×10^{-4}
Methodology × Reagents	−0.3	±0.5	0.50	0.631
Time × Reagents	0	±0.5	0.00	1.000

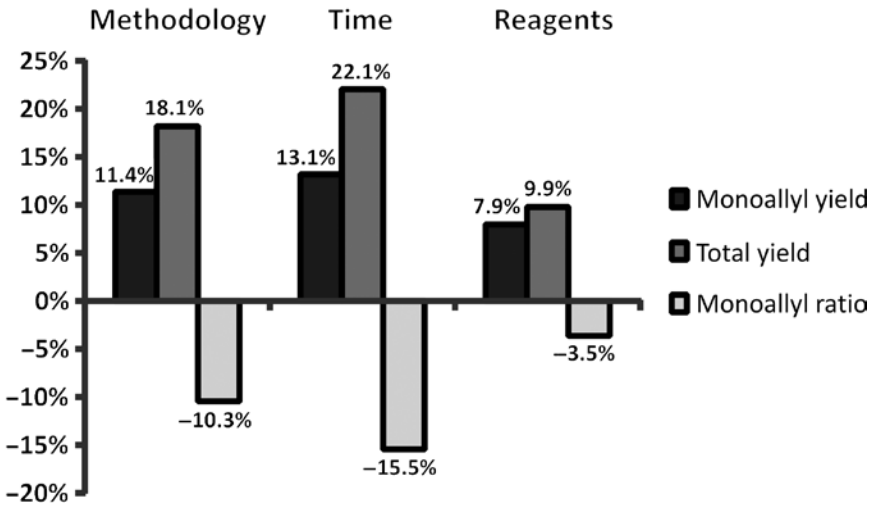

Figure 2: Graphical representation of the effects generated by methodology (conventional to US), reaction time (from 1.5 h to 4 h) and quantity of reagents (7.5 mmol to 10.0 mmol of both allyl bromide and K_2CO_3).

The methodology transposition was evaluated using a 2^3 full factorial design. Methodology (conventional or US), reaction time (1.5 or 4 h) and quantity of reagents (7.5 mmol or 10.0 mmol) were selected as variable factors. Tables 2 and 4 and Figure 2 summarize the results. Among the three factors, quantity of reagents showed a less significant effect in the responses. The transposition from conventional to a US-based methodology showed significant effects on all responses, leading to positive influences on the yields. However, the US methodology led to a negative effect (–10.3%) on the monoallyl ratio. The most important influence is exerted by reaction time, which led to positive effects on monoallyl and total yields, but a negative effect on the monoallyl ratio.

Based on the collected data, US can efficiently speed up the allylation reaction. This characteristic is highly predictable, since we have already reported the acceleration of allylation reaction of 1-naphthol [7]. Although the data in Table 2 suggest that US can decrease the monoallyl ratio, this effect can be explained by the acceleration of the production of *N*-allyl-4-chloroaniline. As can be seen in Table 2, the diallylation only takes place when the monoallylated proportion in the reaction environment is around 30%. Obviously, the production of the *N*,*N*-diallyl-4-chloroaniline is only possible when some amount of *N*-allyl-4-chloroaniline is present in reactional medium. In other words, the distribution of the products is not really affected by US, but in fact, this is an effect of the acceleration of the reaction rate provided by US. The same behavior can be observed regarding time reaction. As long as the reaction is carried out, the greater the production of monoallyl and diallyl products. Data presented in Table 4 corroborate this statement, given that a significant interaction effect on monoallyl ratio has been identified between methodology used and reaction time. As can be seen in Figure 3, the average monoallyl ratio was above 90% even after 4 h of reaction when conventional methodology was used, and below this value when US methodology was employed in only 1.5 h of reaction. However, when the reaction was extended to 4 h, the monoallyl ratio had an average of 74%. Thus, to obtain the best yield with higher monoallyl ratio, the US reaction must be done in 4 h, in lower temperature (i.e. 25°C), and with the use of 7.5 mmol of allyl bromide.

As the results of the 4-h US-based reaction showed comparable yields to the 24-h conventional reaction, we performed a statistical comparison between the results of both approaches (Figure 4). We found that there were

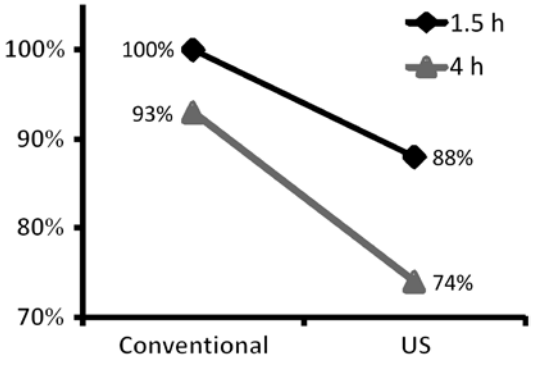

Figure 3: Graphical representation of the interaction effect between time reaction (1.5 h to 4 h) and methodology (conventional and US).

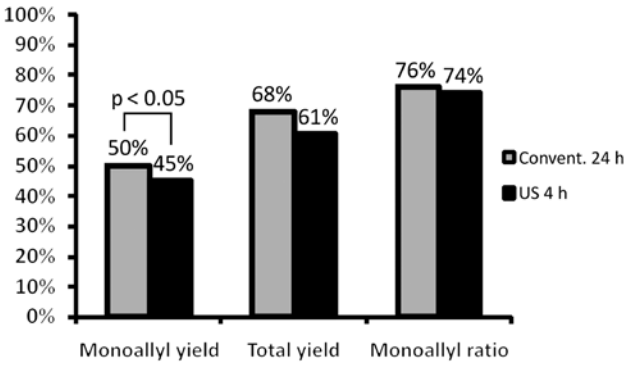

Figure 4: Comparison between the conventional 24-h reaction and US-based 4-h reaction.

significant differences in the monoallyl yield, but no differences were observed in total yield and monoallyl ratio. In summary, this US-based methodology, fully conducted in an ultrasonic bath, can provide the same results as the conventional procedure but in much less time.

4 Conclusions

The experimental results demonstrate that the proposed US methodology can significantly accelerate the synthesis of *N*-allyl-4-chloroaniline, lowering the reaction time from 24 h to only 4 h in the same reaction conditions. Considering the reactions of this work were conducted in an inexpensive ultrasonic bath, without heating and in less time, this study's findings are an important contribution to the development of a more convenient process in laboratorial scale, which can save time and related costs. This methodology can also help achieve some principles of green chemistry, and is useful in other allylation reactions.

Acknowledgments: The authors are grateful to the São Paulo state agency FAPESP (Grant No. 2013/20479-9) and to the Brazilian agency CNPq (Grant No. 455411/2014-0) for providing financial support to this work.

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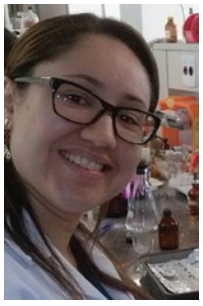

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João Paulo Santos Fernandes

João Paulo Santos Fernandes received his BPharm degree in Pharmacy (2003), his MSc degree (2006), as well as his PhD degree (2012) in Medicinal Chemistry, developing projects in drug design. Prof. Fernandes has worked at several universities in Brazil. Since 2013, he has served as adjunct professor at Federal University of São Paulo (UNIFESP). His research interests include synthesis and evaluation of bioactive compounds, mainly those with activity in the CNS, inflammation, and infectious diseases.