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REACTION OF SOME SALICYL ALDEHYDE DERIVATIVES WITH AMINES ANDPHENYL ACETYLENE

Nguyen Thi Minh Trang[1], Tran Thi Thu Trang[2] and Duong Quoc Hoan[2]*
[1]*Student of the Faculty of Chemistry, Hanoi National University of Education*
[2]*Faculty of Chemistry, Hanoi National University of Education*

Abstract.Salicylic aldehydes, amine, and phenyl acetylene could react under the solvent-free, metal-free conditions to form propargylamines **1**-**4** via A^3 coupling reaction. The yield of the reaction was up to 83% for 5h. In acetonitrile, the amine became a catalyst to form 6-bromo-3-(5-bromo-2-hydroxybenzyl)-2-phenyl-4H-chromen-4-one (**5**). Under microwave conditions, it took about 20 min to complete the reaction and gave the same yields as theconventional method. Structures of these compounds were firm with NMR, MS spectra.

Keywords: propargylamine, multicomponent reaction, aldehyde-alkyne-amine, solvent-free, metal-free.

1. Introduction

The A^3 coupling reaction, a kind of multicomponent reaction, is the term of describing aldehyde-alkyne-amine reaction by Zhao *et al.* in 2011 [1] which is used to make propargylamine derivatives. The A^3 reaction requires a metal catalyst, typically based on ruthenium/copper, gold, or silver [2].

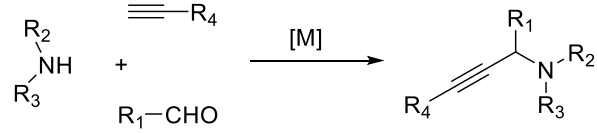

Figure 1. A^3 coupling reaction

However, the drawbacks of these protocols are using metals and organic solvents. For example, in the synthesis of (+) dyoxyline, authors used CuBr, (*R, S*)-N-Pinap, toluene [3]; gold (III) salen complex in the synthesis of Propargylamines [4]; PANF-NHC-Ag in Intramolecular 1,3-Dipolar Cycloaddition [5]. Recently, Basu*et al*. have reported results of A^3 in the case of salicylic aldehyde-alkyne-amine under solvent-free conditions; however, it suffered froma long time of reaction (4 - 8h) [6].

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Contact Duong Quoc Hoan, e-mail address: hoandq@hnue.edu.vn

In this paper, herein, we reported an A^3 coupling reaction of some salicylaldehyde derivatives with amines and phenylacetylene in solvent-free and metal-free conditions using both conventional method and microwave method.

2.Content

2.1. Experimental

2.1.1. Chemicals and equipment

Solvents and chemicals were bought from Sigma-Aldrich (salicylaldehyde), Merck Corp (TLC), Aladdin (piperidine), Vietnam (ethanol, etc.), or other China's companies (morpholine, pyrrolidine, dimethylamine, aniline, cyclohexylamine) were used as received, unless indicated. The NMR spectra were recorded on the BrukerAvance500 MHz NMR spectrometer (at The Vietnam Academy of Science and Technology) in $CDCl_3$. Chemical-shift data for each signal was reported in ppm. Mass spectra were obtained from the Mass Spectrometry Facility of The Vietnam Academy of Science and Technology on LC-MSD-Trap-SL spectrometer. Sharp domestic microwave oven (model: R-21A1(S)VN) was made in Thailand by Sharp Corporation, 2015.

2.1.2. Synthetic procedure

**** 2-(3-phenyl-1-(piperidin-1-yl)prop-2-yn-1-yl)phenol (1)***

- *Conventional method:*

To the mixture of piperidine (1 mmol; 85 mg), salicylaldehyde (1 mmol; 122 mg), phenylacetylene (1 mmol; 102 mg) was refluxed at 90 ^oC for 5h. The progress of reaction was monitored with TLC. The title product was purified with a flash column chromatography with eluent *n*-hexane: ethyl acetate = 15:1 to give a viscous liquid of *2-(3-phenyl-1-(piperidin-1-yl)prop-2-yn-1-yl)phenol* (**1**, 240 mg); ^{1}H-NMR (500 MHz, $CDCl_3$, δ (ppm)):7.56-7.53(3H, m, ArH), 7.36 - 7.34(3H, m, ArH), 7.19 - 7.24 (1H, m, ArH), 6.86 - 6.83(2H, m, ArH), 5.08(1H, s, CHN), 2.72 (4H, brs, 2×CH_2), 1.67(4H, brs, 2×CH_2), 1.50(2H,brs, 1xCH_2).

- *Microwave method:*

The mixture of piperidine (1 mmol; 85 mg), salicylaldehyde (1 mmol; 122 mg), phenylacetylene (1 mmol; 102 mg) was irradiated with the microwave oven at a low power level for 20min. The progress of the reaction was monitored with TLC every 1 min. The workup of the reaction was processed as shown in the conventional method.

**** 2-(1-morpholino-3-phenylprop-2-yn-1-yl)phenol (2)***

Following the procedure for synthesis of compound **1**: morpholine (1 mmol; 87 mg), salicylaldehyde (1 mmol; 122 mg), phenylacetylene (1 mmol; 102 mg) gave a yellow viscous liquid *2-(1-morpholino-3-phenylprop-2-yn-1-yl)phenol* (**2**, 258mg); ^{1}H-NMR (500 MHz $CDCl_3$, δ (ppm)):10.81 (1H, brs, ArOH),7.59 - 7.53(3H, m, ArH), 7.37 - 7.36(3H, m, ArH), 7.25 (1H, m, ArH) 6.89-6.86(2H, m, ArH), 5.12(1H, s, CHN), 3.80 (4H, brs, 2×CH_2O), 2.79(4H, brs, 2×CH_2N).

2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)phenol (3)

Following the procedure for synthesis of compound **1**: pyrrolidine(0.5 mmol; 35.5 mg), salicylaldehyde (0.5mmol; 61 mg), phenylacetylene (0.5 mmol; 61 mg) a yellow viscous liquid *2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)phenol* (**3**, 249mg);

^{1}H-NMR (500 MHz $CDCl_3$, δ (ppm)): 7.55 - 7.50 (3H, m, ArH), 7.34 - 7.31(3H, m, ArH), 7.20 (1H, dt, *J* = 7.2, 0.9 Hz, ArH), 6.85-6.82 (2H, m, ArH), 5.25 (1H, s, CHN), 2.88 - 2.78 (4H, m, 2 × CH_2N), 1.87-1.85 (4H, m, 2 × CH_2).

4-bromo-2-(1-morpholino-3-phenylprop-2-yn-1-yl)phenol (4)

Following the procedure for synthesis of compound **1:** morpholine (0.5 mmol; 43,5 mg), 5-bromo-2-hydroxybenzaldehyde (0.5 mmol; 100,5 mg), phenyl acetylene (0.5 mmol; 51 mg) gave a yellow viscous liquid *4-bromo-2-(1-morpholino-3-phenylprop-2-yn-1-yl)phenol* (**4**, 313mg); ^{1}H-NMR (500 MHz $CDCl_3$, δ (ppm)): 10.9 (1H, brs, ArOH), 7.65 (1H, dd, *J* = 2.0, 0.5, ArH), 7.56 - 7.54(m, 2H, ArH), 7.40 - 7.37(m, 3H, ArH), 7.33 (dd, 1H, *J* = 8.5, 2.0, ArH),6.75(1H, d, *J* = 8.5, ArH), 5.05(1H, s, CHN), 3.80 (4H, brs, 2×CH_2O), 2.77(4H, brs, 2×CH_2N); ^{13}C-NMR **(**125 MHz, $CDCl_3$, δ (ppm))**:**156.3, 132.6, 132.0, 131.5, 129.0, 122.6, 121.9, 118.4, 111.4, 91.0, 80.7, 66.8, 60.4; ESI-MS: $[M-H]^-$ ^{79}Br *m/z* 369,9 ; ^{81}Br 371.9 au.

6-bromo-3-(5-bromo-2-hydroxybenzyl)-2-phenyl-4H-chromen-4-one (5)

To a solution of piperidine (0.5 mmol; 43.5 mg), 5-bromo-2-hydroxybenzaldehyde (0.5mmol; 100.5 mg), phenyl acetylene (0.5 mmol; 51 mg) in 1ml acetonitrile was heated at 85 ºC for 5h. The yellow precipitate was collected and purified with a flash column chromatography with eluent of *n*-hexane: ethyl acetate = 8:1 giving a pale yellow solid *6-bromo-3-(5-bromo-2-hydroxybenzyl)-2-phenyl-4H-chromen-4-one* (**5**, 316mg).^{1}H-NMR (500 MHz $CDCl_3$, δ (ppm)): 8.41 (d, *J* = 2.5 Hz, H5), 7.79 (*dd*, *J* = 2.5, 9.0, H7), 7.37 (d, *J* = 9.0 Hz, H8), 7.59 (m, H11, H15), 7.66 (m, H12, H14), 7.66 (m, H13), 3.84 (s, H16), 6.75 (d, J = 8.5 Hz, H19), 7.11 (dd, *J* = 2.5, 8.5 Hz, H20), 6.26 (d, *J* = 2.5 Hz, H22); ^{13}C-NMR **(**125 MHz, $CDCl_3$, δ (ppm))**:** 165.2 (C1), 121.4 (C2), 179.2 (C3), 123.4 (C4), 128.7 (C5), 119.0 (C6), 137.5 (C7), 120.0 (C8), 155.0 (C9), 132.3 (C10), 129.0 (C11, C15), 131.2 (C12, C14), 129.2 (C13), 25.7 (C16), 127.4 (C17), 154.4 (C18), 119.9 (C19), 131.1 (C20), 111.6 (C21), 133.0 (C22); ESI-MS *m/z* 484.8 (100%).

2.2. Results and discussion

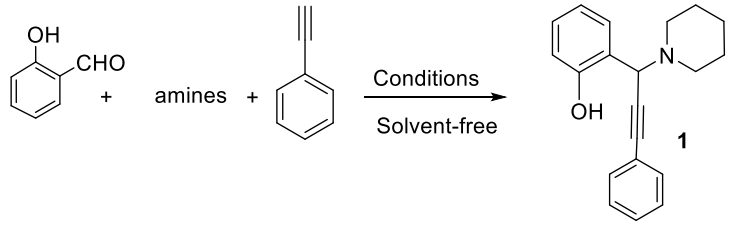
2.2.1. Conventional method

In a preliminary experimental investigation of the optimum reaction conditions regarding the solvent and temperature were screened. For this, salicylic aldehyde (1 mmol), amine (1 mmol), andphenyl acetylene (1 mmol) were chosen as standard model substrates for the synthesis of representative propagylamine **1** via A^3 coupling reaction, Table 1.

The model reaction was carried out with or without 30 mol% of CuI as a catalyst in different bases and various temperatures, Table 1. The first three entries aniline, cyclohexylamine, and dimethylamine did not give any expected products. In contrast, in presence of piperidine and CuI gave product **1** in 83 % yield (entry 4). Because of the highest yield, piperidine was employed for the solvent-free and metal-free case study. First, the model reaction was set at 110 ºC, but the yield was in 72% (entry 5) and slightly lower than the yield of entry 6 that was set at 100 ºC. The temperature was decreased in entries 7 and 8 at 90 and 80 ºC respectively, but the yields of these reactions were maintained at about 83% yield. It could conclude that A^3 coupling

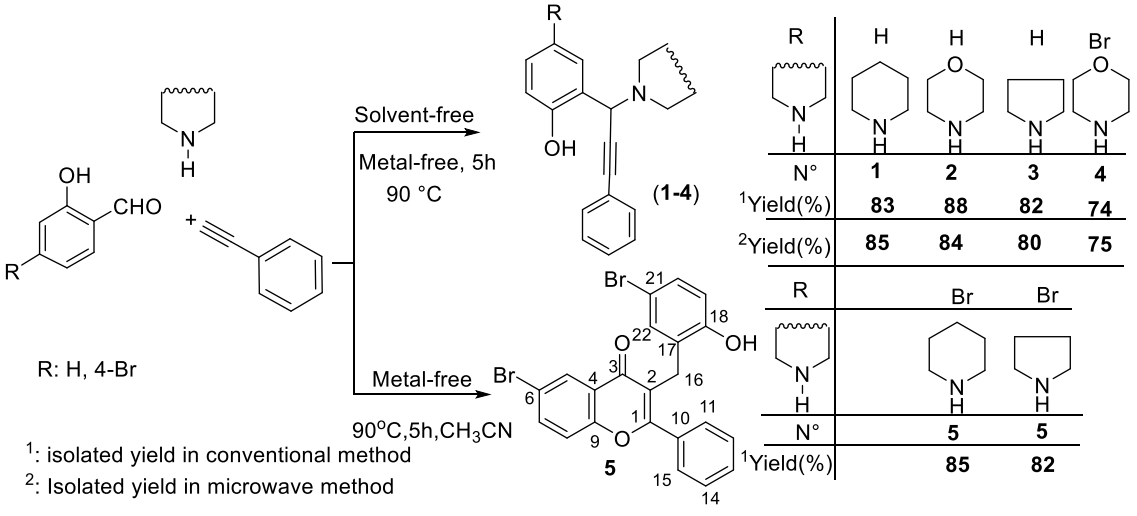
reaction of salicylic aldehyde, amine, and phenylacetylene could work at a lower temperature without CuIcatalyst and solvent. That could explain that without CuI catalyst, the transition state might be weaker than the complex transition state of Cu^{+}.

Table 1. Optimization of A^3 coupling reaction in the conventional method



No.	Catalyst CuI, 30 mol%	Amines	Temperature (°C)	Y (%)*
1	Yes	aniline	110	none
2	Yes	cyclohexylamine	110	none
3	Yes	dimethylamine	110	none
4	Yes	piperidine	110	83
5	No	piperidine	110	72
6	No	piperidine	100	76
7	No	piperidine	90	83
8	No	piperidine	80	83

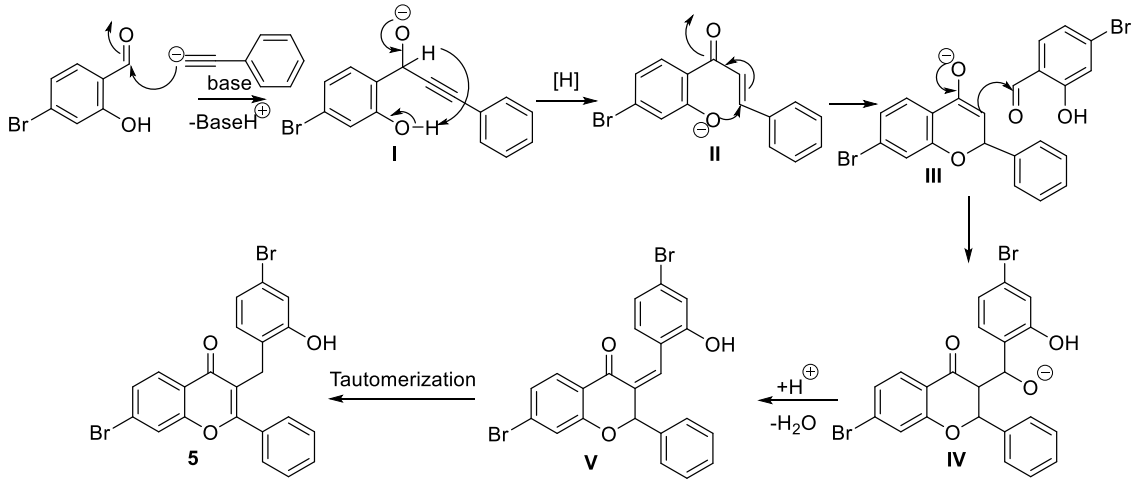
* Isolated yield



Scheme 1. A^3 reaction in both the conventional method and microwave method

So, having the optimized reaction conditions, the scope and efficiency of this approach were explored for the synthesis of propargylamine derivatives **2-4** in 88%, 82%, and 74%, respectively (Scheme 1). We further examined the reaction in CH_3CN; however, compound **5** was obtained in high yield 85% or 82% in presence of piperidine

or pyrrolidine, respectively, Scheme 1. The base frame of bases did not appear in structure **5**. Therefore, bases worked as a catalyst but did not enroll as a reactant. The proposed mechanism was shown in Scheme 2.



Scheme 2. Proposed mechanism

The initial step is believed to be the deprotonation of the phenylacetylene that was a good nucleophile to attach the carbonyl carbon of aldehyde to form intermediate **I**. Electron moving is to promote the formation of hydrogen which did reduction the C≡C to form C=C bond forming intermediate **II**, which facilitates the nucleophilic attack ofphenolate to promote the formation of C-O bond to yield intermediate **III**. Then enolate attached the second aldehyde molecule to yield intermediate **IV**. The subsequent elimination of H_2O molecule *via E1CB* mechanism leads to the formation of intermediate **V.** The final step involves tautomerization of intermediate **V** leads to regeneration of compound **5**, Scheme 2.

Recently, in literature, compound **5** was first synthesized by Lee *et al.* in 2017 [7]; nevertheless, the condition was [Ru] catalyst in presence of CsOAc at 120 ºC. So, our method for synthesis of compound **5** is a promising protocol for green chemistry purposes. Certainly, further conditions for the formation of compound **5** have been being processed.

2.2.2. Microwave method

A^3 reaction of salicylic aldehydes, amines, and phenyl acetylene was further investigated under microwave method with a domestic microwave. Taking advantages of our results in our previous paper [8], the temperature of the reaction was selected basiedon melting points of bases (piperidine (bp = 106 ºC); morpholine (bp = 129 ºC), pyrrolidine (bp = 87 ºC)), hence, low power level and 1- minute-irradiation time were chosen to avoid burning. Then TLC was checked every minute. The results were shown in scheme 1. It found that time of reaction was shortened about 20 minutes, however, the yields of the reaction was not improved comparedwith the conventional method.

The structure of compounds **1-5** was firm with NMR, MS spectral analysis (see experimental section).

3. Conclusions

In conclusion, salicylic aldehydes (1 e.q), amines (1 e.q), and phenyl acetylene (1 e.q) could react to form propargylamines **1÷4** under solvent-free and metal-free conditions via A^3 coupling reaction. The best temperature was found in the range of 80-90 ºC in refluxing. If the mixture was carried out in acetonitrile at the same temperature, the product was 6-bromo-3-(5-bromo-2-hydroxybenzyl)-2-phenyl-4H-chromen-4-one (**5**) in 85% yield instead. The microwave method took 20 min, instead, to get the same yields of propargylamines **1÷4.**

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