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SYNTHESIS OF SOME PROPARGYLAMINES VIA A^3 COUPLING REACTION

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Abstract. Condition for synthesis of propargylamines has been found in highly efficient as a one-pot multi-component protocol. Copper(I) iodide (30% mol) under solvent free condition gave propargylamine in good yields. Structures of propargylamines were elucidated with NMR, MS methods.

Keywords: one-pot multi-component reaction, propargylamine, copper (I) iodide, solvent free, A^3 coupling reaction.

1. Introduction

Propargylamines have recently been used for synthesis of nitrogen-containing compounds such as β-lactam[1, 2], pyrrole [3], pyrrolidine [4], pyrrolophane [5], 3-aminobenzofuran [6], aminoindolizine [7], 2-aminoimidazole [8], oxazolidinone [9], quinoline [10] and multifunctional monoamine oxidase and ChE inhibitors ladostigil (**1**) and PF9601N (**2**) [11, 12].

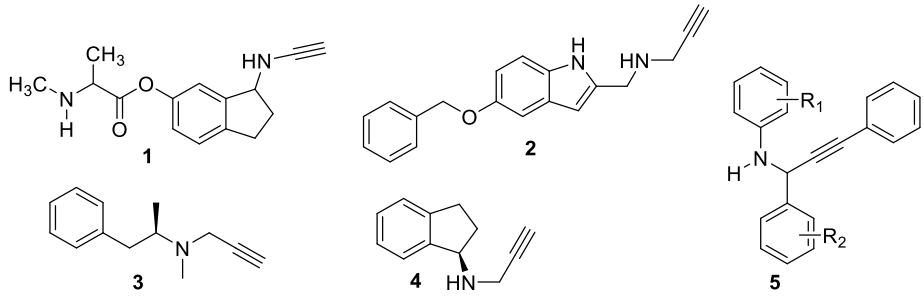

Figure 1. Examples of propargylamines and designed propargylamines

Current treatment options include the use of monoamine oxidase inhibitors like selegiline (**3,** Deprenyl®) and rasagiline (**4,** Azilect®) (Figure 1) in the treatment of Parkinson's disease.

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These drugs are aimed at correcting disturbances in the monoaminergic neurotransmitter system by virtue of inhibiting the monoamine oxidase-B enzyme that is responsible for catalyzing the oxidative degradation of dopamine [13, 14]. Therefore, synthesis of propargylamines has been considered, in which A^3coupling reaction is one of the most popular methods since they are convenient approach, atom economy and eco-friendly reaction condition. In order to take advantages of A^3coupling reaction in the synthesis of propargylamine derivatives, herein, we wish to report an optimized condition and synthesis of four new propargylamine derivatives (**5**) via A^3 coupling reaction, Figure 1.

2. Content

2.1. Experimental

2.1.1. Chemicals and equipment

Solvents and chemicals were bought from Sigma-Aldrich (phenylacetylene), Merck Corp (*m*-nitroaniline), Aladdin (*p*-bromoaniline), Vietnam (ethanol), or other China's companies (aniline) were used as received unless indicated. The NMR spectra were recorded on the Bruker Avance 500 MHz NMR spectrometer in DMSO-d_6. 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.

2.1.2. Synthetic procedure

*N-(1-phenyl-3-phenyl-2-propynyl)-aniline (**5a**)*

A mixture of aniline (1.0 mmol, 121.5 mg), benzaldehyde (1mmol; 115.6 mg), phenylacetylene (1.1 mmol; 112.3 mg), CuI (1% mol; 22.3 mg) was heated at 110^{o}C for 8h. The progress of reaction was monitored with TLC. The title product was purified with a flask column in eluent *n*-hexane: ethyl acetate = 20:1 in 83% yield. ^{1}H NMR (500 Hz, $CDCl_3$, δ ppm): 7.65 (d, *J* = 7.5Hz, 2 H), 7.39 (t, *J* = 8.0 Hz, 4H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.5 Hz, 3H), 7.19 (t, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 7.5 Hz, 3H), 5.49 (s, 1H), 4.10 (br, 1H); ^{13}C NMR (125 Hz, $CDCl_3$, δ ppm): 147.5, 146.0, 129.4, 128.5, 128.45, 128.4, 128.2, 126.9, 126.7, 122.7, 120.8, 113.5, 88.8, 85.7, 54.5; +MS = 283.8 au (100%).

*N-(1-phenyl-3-phenyl-2-propynyl)-m-nitroaniline (**5b**)*

Following the procedure of **5a**: *m*-nitroaniline (0.3 mmol; 42.1 mg), benzaldehyde (0.3 mmol; 38.4 mg), phenylacetylene (0.33 mmol, 56.5 mg), CuI (30% mol, 25.3 mg), 12 h, *n*-hexane: ethyl acetate = 10:1, 85% yield.^{1}H NMR (500 Hz, $CDCl_3$, δ ppm): 7.66-7.64 (m, 3 H), 7.62 (ddd, *J* = 1.0, 2.5, 8.0 Hz, 1 H), 7.45-7.35(m, 5 H), 7.33- 7.25(m, 4 H), 7.02 (ddd, *J* = 1.0, 2.5, 8.0 Hz, 1 H), 5.49 (d, *J* = 1.5 Hz, 1H), 4.49 (d, *J* = 1.5Hz, 1 H); ^{13}C NMR (125 Hz, $CDCl_3$, δ ppm): 149.2, 147.2, 138.5, 131.8, 129.7, 128.6, 128.5, 127.3, 122.3, 119.8, 113.2, 108.1, 86.9, 85.4, 50.4 (ppm); +MS = 328.9 au (100%).

*N-[1-(4-methoxiphenyl)-3-phenyl-2-propynyl]-m-nitroaniline (**5c**)*

Following the procedure of **5a**: *p*-methoxyaniline (0.3 mmol, 42.8 mg), *p*-methoxibenzaldehyde (0.3 mmol, 42.3 mg), phenylacetylene (0.33 mmol, 50.8 mg), CuI (30% mol, 20.0 mg), 110^{o}C, 12h, *n*-hexane: ethyl acetate = 10:1, 74% yield; ^{1}H NMR

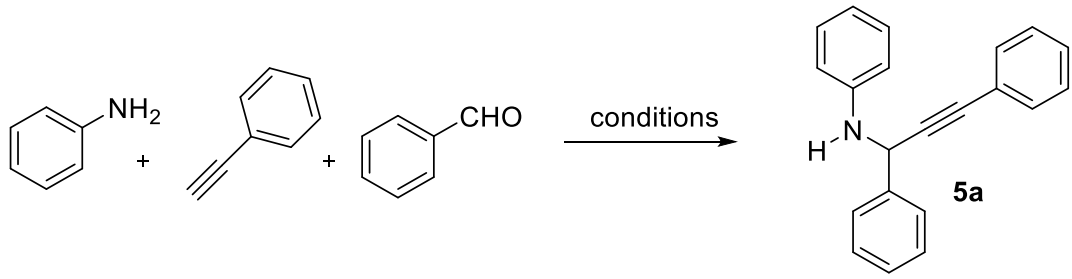
(500 Hz, $CDCl_3$, δ ppm): 7.64 (t, *J* = 7.5 Hz, 1H), 7.61(dd, *J* = 8.0, 1.5 Hz, 1H), 7.57(d, *J* = 8.5Hz, 2H), 7,41(dd, *J* = 8.0, 1.5 Hz, 2H); 7,33(d, *J* = 8.5 Hz, 2H), 7.31 (s, 1H), 7.28 (t, *J* = 8.5Hz, 1H), 7.03 (dd, *J* = 2.0, 8.5Hz, 2H), 6.95 (d, *J* = 8.5Hz, 2H), 5.50 (d, *J* = 5.5 Hz, 1H) 4.44 (d, *J* = 5.5Hz,1H), 3.83 (s,3H); ^{13}C NMR (125 Hz, $CDCl_3$, δ ppm): 159.7, 149.2, 147.2, 131.7, 130.5, 129.6, 128.6, 128.5, 128.3, 122.3, 119.8, 114.3, 113.1, 108.0, 87.2, 85.7, 55.3, 49.8; +MS = 358.9 au (100%).

*N-[1-(4-methoxiphenyl)-3-phenyl-2-propynyl]-p-bromoaniline (**5d**)*

Following the procedure of **5a**: *p*-bromoaniline (0.3 mmol, 54.7 mg), *p*-methoxibenzaldehyde (0.3 mmol, 51.7 mg), phenylacetylene (0.33 mmol, 53.5 mg), CuI (30% mol, 24.9 mg), 110°C , 12h, *n*-hexane: ethyl acetate = 10:1, 70% yield; ^1H NMR (500 Hz, $CDCl_3$, δ ppm): 7.55 (d, *J* = 8.0 Hz, 2H), 7.41-7.39 (m, 2H), 7.30-7.26 (m, 5H), 6.93 (d, *J* = 8.5Hz, 2H), 6.66 (d, *J* = 8.0Hz, 2H), 5.39 (s,1H), 4.13 (br, 1H), 3.83 (s,3H); ^{13}C NMR (125 Hz, $CDCl_3$, δ ppm): 159.5, 145.5, 131.8, 131.7, 131.3, 128.5, 128.4, 128.2, 122.6, 115.7, 114.2, 110.3, 88.1, 85.1, 55.2, 50.0; +MS = 391.8 au (100%); 393.8 au (94%).

2.2. Results and discussion

In order to find a condition that is appropriate to our case, the A^3 model reaction was carried out with 30 mol% of each catalyst in different solvents or solvent free at 110°C or at boiling point of the solvent, Scheme 1, Table 1, [15]. Anhydrous $FeCl_3$ (entry 2) seemed to be more effective than the hydrate form of $FeCl_3$ as the yield of entry 1 was slightly smaller. In entry 3, ethanol was added, but the yield of the reaction stayed the same as in entry 1. Another catalyst, a mixture of copper sulfate and glucose promoted dramatically reaction forward to the product in 70% yield in ethanol solvent (entry 4). However, as heated without solvent, entry 5 gave a bit better yield (75%). Thus, it is concluded that there is no need for the solvent to carry out the reaction this reaction and solvent-free is the best condition for the synthesis of propargylamines via A^3. Further, $SnCl_2.2H_2O$ (entry 6), $ZnCl_2.2H_2O$ (entry 7), and $FeCl_2.4H_2O$ (entry 8) in solvent free condition gave yields of 61, 50, 45 yield, respectively. In the presence of CuI under solvent-free conditions (entry 9) also performed better than in methanol (entry 10). We could include that CuI under solvent free condition was suitable for our case, Scheme 1.



Scheme 1. The A³ model reaction for optimizing

Table 1. Optimization of catalyst

No.	Catalyst	Solvent	Yield (%)*
1	$FeCl_3.3H_2O$	-	42
2	$FeCl_3$ (anhydrous)	-	54
3	$FeCl_3.3H_2O$	Ethanol	42
4	$CuSO_4$ + glucose	Ethanol	70
5	$CuSO_4$ + glucose	-	75
6	$SnCl_2$. $2H_2O$	-	61
7	$ZnCl_2.2H_2O$	-	50
8	$FeCl_2.4H_2O$	-	45
9	CuI	-	83
10	CuI	Methanol	68

** Isolated yield*

To optimize the concentration of catalyst, we further examined the influence of catalyst concentration on the reaction time and percentage yield. So, the model reaction was performed using different concentration of catalyst 5, 10, 15, 20, 25, 30, 35 mol% of CuI at 110°C under solvent-free conditions and the product **5a** was obtained in 40, 52, 59, 69, 73, 83 and 83 % yields, respectively. Further, the yield of the product did not improve as the concentration of catalyst increased, Table 2.

Table 2. The effect of catalyst loading on the model

Entry	Catalyst (mol %)	Isolated Yield (%)
1	5	40
2	10	52
3	15	59
4	20	69
5	25	73
6	30	83
7	35	83

Using optimized condition, three propargylamines were synthesized in good yields (see experimental), Figure 2.

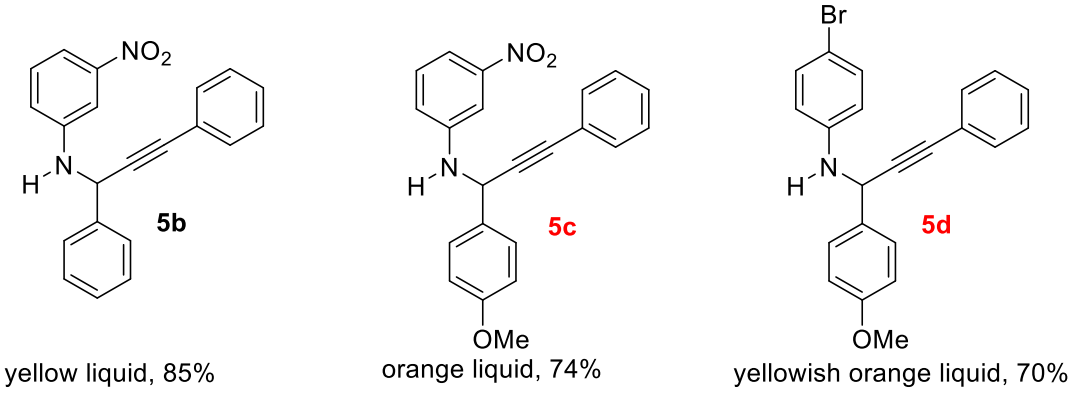


Figure 2. Synthesized propargylamines

3. Conclusions

In conclusion, highly efficient, the one-pot multi-component protocol has been developed for the synthesis of some propargylamines using copper(I) iodide (30% mol) under the solvent free conditions in good yields. Four propargylamines were synthesized in up to 85% yield. Structures of propargylamines were firm with NMR, MS methods.

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