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# AgY zeolite as catalyst for the effective three-component synthesis of propargylamines

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## Abstract

The preparation of substituted propargylamines via three-component reaction between aldehydes, terminal alkynes, and secondary amines following an environmentally acceptable methodology has been developed. The process has been carried out under solvent-free conditions in the presence of AgY zeolite. The catalyst can be easily recovered and reused for at least four cycles without significant decreases in yield and selectivity.

## 1. Introduction

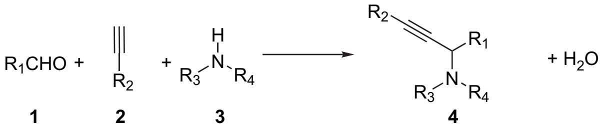
Great efforts have been devoted in the last decade to the re-examination of the most important synthetic processes in the light of the new stringent and growing environmental regulations.[1] As a consequence, the development of more eco-compatible methodologies is needed. To this purpose heterogeneous catalysis can play an important role.[2] The advantages derived from the use of this kind of catalysis are low corrosion, minimum execution time, waste minimization, easy transport, and disposal of catalysts[3] to name but a few, with benefits from both economic and environmental points of view.

As a consequence, there has been a great development of supported catalysts for performing laboratory- and industrial-scale reactions.[4] In fact, the anchoring of a homogeneous catalyst to the surface of an inorganic or organic material allows the easy removal of the catalyst by filtration before the reaction mixture is worked-up, its reuse and the increasing of its life by avoiding deactivation (i.e., by aggregation of active sites).

In continuation of our investigations on the use of heterogeneous catalysts for fine chemical preparation through multicomponent procedures[5] and by using eco-compatible solvents, here we present our recent studies on the synthesis of substituted propargylamines via three-component reaction between aldehydes, terminal alkynes, and secondary amines in the presence of a silver exchanged Y zeolite, under solvent-free conditions.

## 2. Results and discussion

Substituted propargylamines **4** are important intermediates for fine chemical and pharmaceutical preparations;[6] they are usually synthesized by reacting aldehydes **1**, terminal alkynes **2**, and secondary amines **3** (Scheme 1).



Scheme 1. Three-component synthesis of propargylamines.

The reaction itself is an environmentally benign process as it combines the advantages of multicomponent synthesis,

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utilized to assemble three or more starting compounds into the target molecule in one reaction vessel,[7] with an high atom economy (up to 95%),[8] water being the sole by-product produced during the whole synthesis.

The reaction is usually promoted by copper,[9] silver,[10] and gold salts[11] in water and a large variety of propargylamines can be obtained in very good yields and with small amounts of catalyst (1–3%). Of course, by operating under homogeneous conditions, two main drawbacks must be considered: the difficulty to recover and reuse the catalyst and the possible absorption of some of the metal catalyst from the final product. To this regard it must be reminded that presently the upper tolerance limit for the contamination of drugs or other compounds set aside for human consumption by transition metals is 5 ppm and that future regulation is expected to lower this threshold to the ppb range.

Only few studies have been reported in the literature concerning the use of supported metal catalysts for the three-component preparation of propargylamines. These include the use of hydroxyapatite-supported copper,[12] 12-tungstophosphoric acid-supported silver,[13] and layered double hydroxide-supported gold.[14] Nevertheless, due to the increasing demands of the environmental legislations, the development of methodologies employing solid and easy recyclable catalysts and green solvents or better solventless conditions is still needed.

Based on literature data, we have envisaged to catalyze the process with metal-doped zeolites. Three kind of catalysts, namely copper-,[15] silver-,[16] and gold-exchanged[17] NaY zeolites were prepared following well known methodologies reported in the literature; the ICP analyses of Cu–NaY zeolite, Ag–NaY zeolite, and Au–NaY zeolite revealed the following metal doping: 1.14, 2.43, and 0.28 mmol/g, respectively.

The catalysts were tested in the model reaction performed by mixing equimolar amounts of benzaldehyde **1a**, phenylacetylene **2a**, and piperidine **3a** and by heating the neat mixture under a nitrogen atmosphere at 100 °C for 5 h (the amount of the three doped zeolites was selected on the basis of their loading value in order to introduce 10% of active catalyst in all experiments). The results of these experiments are collected in Table 1; for comparison the reaction for the synthesis of propargylamine **4aaa** was also carried out in the presence of the undoped zeolite NaY.

Table 1
Catalyst effect in the three-component propargylamine **4aaa** synthesis

| Entry | Catalyst | **4aaa** Yield (%) | **4aaa** Selectivity[a] (%) |
|---|---|---|---|
| 1 | NaY | 4 | 95 |
| 2 | Cu–NaY | 43 | 96 |
| 3 | Ag–NaY | 52 | 92 |
| 4 | Au–NaY | 32 | 96 |

[a] Selectivity=yield/conversion×100.

Undoped zeolite NaY (entry 1) is not able to promote the process in satisfactory yield, AuY zeolite affords the product in low yield whereas both Cu–NaY and Ag–NaY catalysts produce propargylamine **4aaa** in moderate yields (43 and 52%, respectively).

In order to verify the real heterogeneity of the process, we performed the Sheldon test[18] on the reactions carried out with the three doped catalysts with the aim of evaluating possible metal leaching. Thus the reaction mixture was filtered at 100 °C after 2 h and the filtrate was further heated at 100 °C for additional 3 h. Moreover, benzaldehyde, phenylacetylene, and piperidine were added to the recovered solid catalysts and the mixture was heated at 100 °C for 5 h.

Results from Table 2 show that Cu–NaY and Au–NaY catalysts leaches some metal ions into the solution during the reaction; on the contrary, Ag–NaY zeolite is able to promote the process without leaching the metal into the solution and consequently the catalytic process can be considered truly heterogeneous. It is well known that copper ions can form strong complexes with amines and acetylenes[19] and consequently they can be easily sequestered by phenylacetylene, piperidine or the product itself under the above reaction conditions. Gold leaching can be ascribable to the fact that gold is a trivalent cation and probably is not stable in the zeolite framework; in addition gold is reported to form stable complexes with phenylacetylenes[20] and consequently it can be easily leached from the zeolite.

Table 2
Sheldon test on the reactions carried out with the Cu-, Ag-, and Au-doped zeolites

| Entry | Catalyst | **4aaa** Yield (%) | | |
|---|---|---|---|---|
| | | 2 h | 2+3 h | Reused catalyst |
| 1 | Cu–NaY | 20 | 43 | 31 |
| 2 | Ag–NaY | 26 | 27 | 50 |
| 3 | Au–NaY | 18 | 32 | 13 |

Thus, Ag-NaY zeolite was utilized for the reaction optimization. The following parameters were considered: reaction time, reaction temperature, reagent molar ratio, and catalyst amount.

First of all the model reaction was analyzed comparing the yield of product **4aaa** versus time by carrying out the reaction for 20 h and performing GC analyses at 2.5 h intervals (Fig. 1).

Results confirm that the maximum production of **4aaa** occurs during the first 5 h (∼50% yield), while subsequently the reaction proceeds slowly and the maximum yield value (∼70%) is reached after 15 h.

The effect of the reaction temperature was then examined. The process was carried out at 80 and 100 °C (open flask) and

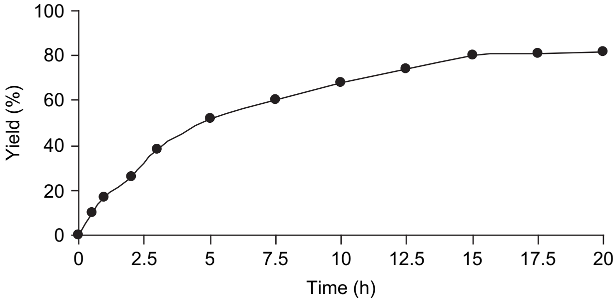


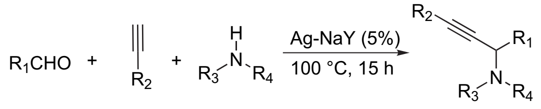
Figure 1. Reactivity of benzaldehyde, phenylacetylene, and piperidine in the presence of Ag–NaY zeolite at 100 °C as a function of time.

Table 3
Temperature effect in the three-component propargylamine **4aaa** synthesis

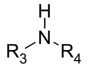
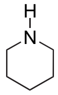
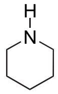
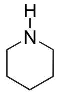
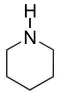
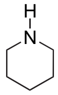
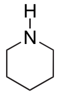
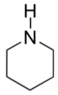
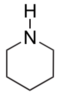
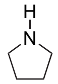
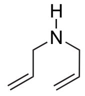
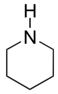
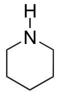
| Entry | Temperature (°C) | **4aaa** Yield (%) | **4aaa** Selectivity[a] (%) |
|---|---|---|---|
| 1 | 80 | 65 | 93 |
| 2 | 100 | 80 | 92 |
| 3 | 120 | 83 | 91 |
| 4 | 140 | 81 | 89 |

[a] Selectivity=yield/conversion×100.

Table 4
Three-component synthesis of substituted propargylamines **4**



**1** **2** **3** **4**

| Entry | $R_1$ | $R_2$ |  | Product | Yield (selectivity[a]) [%] |
|---|---|---|---|---|---|
| 1 | Ph | Ph |  | **4aaa** | 81 (91) |
| 2 | 4-OMe$C_6H_4$ | Ph |  | **4baa** | 72 (91) |
| 3 | 4-Cl$C_6H_4$ | Ph |  | **4caa** | 73 (93) |
| 4 | 3-Cl$C_6H_4$ | Ph |  | **4daa** | 42[b] (96) |
| 5 | Ph | 4-Cl-Ph |  | **4aba** | 77 (91) |
| 6 | Ph | 4-$^t$Bu-Ph |  | **4aca** | 97 (99) |
| 7 | Ph | Hexyl |  | **4ada** | 79 (94) |
| 8 | Ph | Octyl |  | **4aea** | 62 (93) |
| 9 | Ph | Ph |  | **4aab** | 85 (90) |
| 10 | Ph | Ph |  | **4aac** | 50 (91) |
| 11 | Ph$(CH_2)_2$ | Ph |  | **4eaa** | 78 (91) |
| 12 | $Et_2CH$ | Ph |  | **4faa** | 84 (93) |

[a] Selectivity=yield/conversion×100.
[b] Carried out with 10% Ag–NaY.

at 120 and 140 °C (autoclave)[21] for 15 h. Results are reported in Table 3.

1-(1,3-Diphenyl-prop-2-ynyl)-piperidine **4aaa** was obtained with good selectivity in all the reactions. Nevertheless, a decrease in reaction temperature from 100 to 80 °C afforded the product with lower yield (65%), while only a little yield improvement was observed when the temperature was raised to 120 °C (from 80 to 83%).

In subsequent experiments, the reagent molar ratio was varied. Reactions were carried out with the following benzaldehyde/phenylacetylene/piperidine ratios: 1.0:1.0:1.0, 1.0:1.5:1.2, and 1.0:1.2:1.5. Propargylamine **4aaa** was isolated in 80, 60, and 57% yields, respectively, confirming that contrary to the results reported under homogeneous catalysis,[10] under heterogeneous conditions the process allows the isolation of the product with the best yield by using an equimolar amount of the reagents.

The effect of the catalyst amount on the reaction yield was also examined. It was observed that at 100 °C, the model reaction took place also with a lower amount (5% Ag content) of catalyst: the same good yield (81%) of **4aaa** was obtained. Below this quantity of catalyst (2% Ag content), a considerable yield drop was observed (60%).

The process was then utilized for the preparation of variously substituted propargylamines by reacting an equimolar amount of aldehydes, terminal alkynes, and secondary amines at 100 °C under nitrogen for 15 h in the presence of 5% Ag–NaY zeolite (Table 4). In all cases, propargylamines were isolated in good yield and selectivity. No substantial different reactivity was observed when benzaldehydes carrying groups of different electronic nature at the *para* position were employed, the corresponding propargylamines being obtained with the similar yield (compare entries 2 and 3 of Table 4). This can be ascribable to the fact that the iminium ion formation from the aldehyde and the secondary amine (first step of the reaction) is very fast and it is independent from the nature of the aromatic aldehydes.[22] This statement is confirmed by the results obtained by carrying out the reaction with aliphatic enolizable aldehydes (Table 4, entries 11 and 12): the corresponding propargylamines were obtained with good yield (78–84%) and a good selectivity (91–93%) with only traces (∼2%) of the self-condensation product.

By using phenylacetylenes carrying substituents on the aromatic ring with different electronic properties, different yields in the final products were achieved. This can be rationalized by considering that electron-donating groups at the *para* position enhance the nucleophilic character of the phenylacetylene–silver derivatives (Table 4, entry 5), whereas when electron-withdrawing groups are present (Table 4, entry 4) an opposite effect was found. As expected, the use of *N*,*N*-diallylamine with a lower nucleophilicity than the cyclic amines, affords the corresponding propargylamine **4aac** in modest yield (Table 4, entry 10).

In all cases, after each cycle, the silver zeolite can be simply recovered by filtration, washed with ethyl acetate, dried at 300 °C, and reused in a successive batch. No remarkable decrease in yield and selectivity was detected for at least four reaction cycles [yield (selectivity) for the model reaction: first cycle 81% (91%), second cycle 76% (92%), third cycle 77% (92%), fourth cycle 75% (91%)].

## 3. Conclusions

In conclusion we have shown that Ag–NaY zeolite can be utilized as an efficient heterogeneous catalyst for the eco-efficient preparation of propargylamines following a three-component strategy. Moreover, the absence of VOC (a solvent is required only in the work-up procedure for catalyst filtration and washing), the easy preparation of Ag–NaY zeolite (from commercial NaY zeolite and silver nitrate) and the possibility to recycle the catalyst for at least four times with the same good yield and selectivity, makes this approach practical and environmentally acceptable.

## 4. Experimental

### *4.1. Material and reagents*

NaY zeolite HSZ-320 (Tosoh Corp.) is a FAU zeolite with 5.6 $SiO_2/Al_2O_3$ molar ratio, pore size 7.4 Å and surface area 570±10 $m^2/g$.

The Cu–NaY zeolite was prepared by a conventional ion exchange method[15] in which NaY was treated with an aqueous solution of cupric nitrate at 90 °C for 5 h, washed with deionized water, filtered, dried, and calcined at 500 °C for 15 h in air; loading 1.14 mmol/g.

The Ag–NaY zeolite was prepared by a conventional ion exchange method[16] in which NaY was treated with an aqueous solution of silver nitrate at room temperature for 5 h in a dark, washed with deionized water, filtered, dried, and calcined at 500 °C for 15 h in air; loading 2.43 mmol/g.

The Au–NaY zeolite was prepared by a conventional ion exchange method[17] in which NaY was treated with an aqueous solution of chloroauric acid (maintaining the pH value between 5 and 6 through aqueous sodium hydroxide addition) at 80 °C for 2 h, washed with deionized water, filtered, dried, and calcined at 500 °C for 15 h in air; loading 0.28 mmol/g.

Benzaldehyde was distilled under reduced pressure and stored in a bottle under nitrogen and in the dark before use. All other organic reagents were commercial products (Aldrich, Fluka) and were used as such.

### *4.2. ICP measurement*

ICP measurements were carried out on an ICP-AES Jobin Yvon mod. 2501 Ultima 2 spectrophotometer by preparing samples dissolving 50 mg of calcined exchanged Y zeolite in concentrated nitric acid.

### *4.3. General procedures for the three-component synthesis of propargylamines (**4**)*

The three-component reaction was performed by stirring under nitrogen atmosphere a mixture of the selected benzaldehyde (5 mmol), the selected secondary amine (5 mmol), the selected alkyne (5 mmol), and the Ag–NaY zeolite (0.1 g) at 100 °C for 15 h. After cooling to room temperature the mixture was filtered using a Büchner funnel and the zeolite was washed with ethyl acetate (30 ml). The crude product was then purified through a silica gel column (length: 25 cm, diameter: 4 cm) using mixtures of $CH_2Cl_2$/MeOH (99:1 to 95:5) as eluant. Spectral data of known propargylamines **4aaa**, **4baa**, **4caa**, **4daa**, **4aab**, **4aac**, **4eaa**, and **4faa** were in accordance with literature data.[10,11]

#### *4.3.1. 1-(3-(4-Chlorophenyl)-1-phenylprop-2-ynyl)piperidine (**4aba**)*

Dark yellow solid; mp 55.5–57.5 °C; IR (neat): 2260 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.39–1.50 (m, 2H), 1.52–1.70 (m, 4H), 2.50–2.62 (m, 4H), 4.79 (s, 1H), 7.25–7.48 (m, 7H), 7.61 (d, $J$=7.2 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 138.17, 133.97, 132.96, 128.52, 128.43, 128.04, 127.49, 121.70, 87.11, 86.63, 62.30, 50.65, 26.04, 24.31; MS (EI, *m/z*) 309 ($M^+$, 25), 234 (73), 255 (100), 189 (31). Anal. Calcd for $C_{20}H_{20}ClN$: C, 77.74; H, 6.52; N, 4.53. Found: C, 77.68; H, 6.56; N, 4.44.

#### *4.3.2. 1-(3-(4-tert-Butylphenyl)-1-phenylprop-2-ynyl)piperidine (**4aca**)*

Pale yellow solid; mp 56.5–59.0 °C; IR (neat): 2210 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.32 (s, 9H), 1.39–1.50 (m, 2H), 1.53–1.67 (m, 4H), 2.52–2.61 (m, 4H), 4.79 (s, 1H), 7.26–7.40 (m, 3H), 7.35 (d, $J$=8.4 Hz, 2H), 7.46 (d, $J$=8.4 Hz, 2H), 7.63 (d, $J$=7.3 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 151.23, 138.60, 131.45, 128.50, 127.95, 127.33, 125.20, 120.25, 87.81, 85.21, 62.31, 50.56, 34.68, 31.13, 26.09, 24.37; MS (EI, *m/z*) 331 ($M^+$, 42), 254 (82), 247 (100), 217 (32). Anal. Calcd for $C_{24}H_{29}N$: C, 87.09; H, 8.83; N, 4.23. Found: C, 86.99; H, 8.86; N, 4.32.

#### *4.3.3. 1-(1-Phenylnon-2-ynyl)piperidine (**4ada**)[14]*

Yellow oil; IR (neat): 2254 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (t, $J$=6.8 Hz, 3H), 1.24–1.68 (m, 14H), 2.28–2.53 (m, 6H), 4.55 (s, 1H), 7.23–7.41 (m, 3H), 7.57 (d, $J$=7.1 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 139.04, 128.47, 127.81, 127.13, 87.88, 76.137, 61.91, 50.43, 31.78, 29.21, 29.03, 29.00, 28.86, 26.06, 24.41, 22.62, 18.75, 14.06; MS (EI, *m/z*) 283 ($M^+$, 8), 206 (100), 128 (16). Anal. Calcd for $C_{20}H_{29}N$: C, 84.88; H, 10.33; N, 4.95. Found: C, 84.97; H, 10.36; N, 4.90.

#### *4.3.4. 1-(1-Phenylundec-2-ynyl)piperidine (**4aea**)[14]*

Yellow oil; IR (neat): 2253 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.89 (t, $J$=6.7 Hz, 3H), 1.22–1.66 (m, 18H), 2.28–2.53 (m, 6H), 4.55 (s, 1H), 7.22–7.41 (m, 3H), 7.56 (d, $J$=7.4 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 139.08, 128.44, 127.78, 127.09, 87.83, 76.15, 61.90, 50.43, 31.25, 28.95, 28.51, 26.07, 24.39, 22.53, 18.73, 13.98; MS (EI, *m/z*) 311 ($M^+$, 5), 234 (71), 130 (100), 115 (40). Anal. Calcd for $C_{22}H_{33}N$: C, 84.97; H, 10.70; N, 4.50. Found: C, 84.88; H, 10.66; N, 4.41.

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21. Piperidine boiling point=104–105 °C.
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