Mechanistic studies on the metal-free decarboxylativecoupling reaction for synthesis of propargylamines by NMR

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Abstract

Metal-free decarboxylative coupling reaction of phenylpropiolic acid, paraformaldehyde, and morpholine was monitored by NMR spectroscopy (^{1}H, ^{13}C NMR, NOE, DOSY, COSY HMBC, and HSQC). Hemiaminal and bisaminal were obtained from the reaction with paraformaldehyde and morpholine. The resulting hemiaminal was more reactive than the corresponding bisaminal in the reaction with phenylpropiolic acid. The decarboxylative coupling with hemiaminal and phenylpropiolic acid may be the major pathway, producing the desired phenylpropargylamine.

Keywords: Mechanism, NMR, decarboxylative coupling, propiolic acids, propargylamines

Introduction

In recent years metal-catalyzed decarboxylative coupling reactions have received much attention in organic chemistry.[1,2] As the starting materials, carboxylic acids, are stable and environmentally friendly because they release nontoxic carbon dioxide as the by-product in the coupling reactions. The decarboxylative coupling reaction with aromatic carboxylic acids has been developed since Goossen first reported Pd-catalyzed decarboxylative coupling in 2007.[3] We first reported the Pd-catalyzed decarboxylative coupling of alkynylcarboxylic acids in 2008.[4,5] Since then, several related methods have been independently developed by us and other groups.[6-16] The decarboxylative coupling of alkynylcarboxylic acids showed a similar reaction pattern to the Sonogashira reaction of terminal alkynes. Therefore, alkynylcarboxylic acids have been used as the surrogates of terminal alkynes in the coupling reactions and three-component reactions.[17-21] In particular, propiolic acid has been widely used as a source of acetylene because it can be easily handled and stored.

Propargylamine is one of the important building blocks in the synthesis of heterocyclic molecules containing a nitrogen atom.[22-29] Several synthetic methods have been developed.[30-33] The metal-catalyzed three-component reaction of an alkyne, amine, and aldehyde is one of the frequently used methods because it is simple and straightforward; Zn, Rh, Fe, In, Cu, Co, Au, and Ag, for examples, have been used as metal catalysts.[34-45]

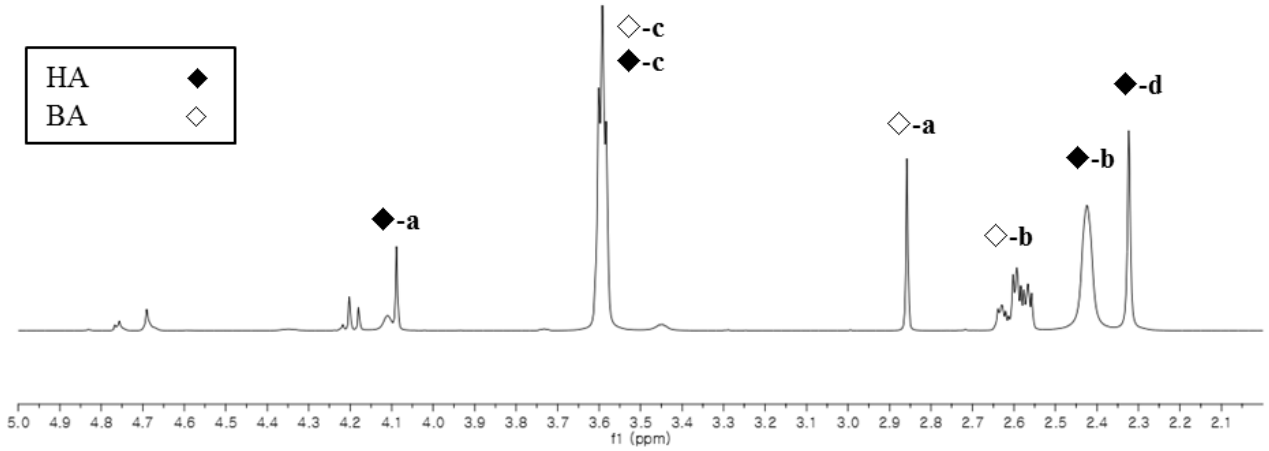
Recently, we reported the Cu-catalyzed three-component reaction of arylalkynylcarboxylic acids with aldehydes and amines to provide the corresponding propargyl amines.[46] This three-component coupling provides the desired products even in the absence of metal catalysts when paraformaldehyde is used.[47] This report was the first example of the metal-free decarboxylative coupling reaction of alkynylcarboxylic acids. In continuation of our efforts to develop decarboxylative coupling reactions and investigate their reaction pathways, a systematic study was conducted on the mechanism of metal-free synthesis of propargylamines. Herein, we report NMR studies on the reaction pathways to the decarboxylative coupling with phenylpropiolic acid (PPA), paraformaldehyde, and amine (morpholine).

Results and Discussion

In the metal-free three-component reaction, we expect that the formation of an aldimine is the initial reaction step.[48,49] When formaldehyde and morpholine were reacted at 25 °C in CD_3CN, both hemiaminal (**HA**) and bisaminal (**BA**) were formed in 56 and 44% yields, respectively, in the reaction mixture as shown by the ^{1}H NMR analysis (Figure 1a and Table 1). The experiment was carried out without any drying process for the reagents. All the peaks were assigned by 2D NMR analysis (see Supplementary Material, Figure S1). The singlet peaks of the methylene protons in **HA** and **BA** appeared at 4.09 and 2.86 ppm, respectively, in the ^{1}H NMR spectra. When the amount of morpholine was doubled, and the ratio of paraformaldehyde to morpholine was 1:2, only **BA** was observed in the ^{1}H NMR spectrum of the reaction mixture. When the temperature was increased to 65 °C, **HA** and **BA** reached the equilibrium state (**HA** = 60% and **BA** = 40%).

We added an equal amount of phenylpropiolic acid (**PPA**) into this resulting mixture and monitored the progress of the reaction by ^{1}H and ^{13}C NMR (Figure 2). Interestingly, the desired product, phenylpropargylamine (**PGA**), was formed in 40% yield in 10 min after adding the **PPA**. However, there was no further increase in this product after a further 24 h at room temperature. As shown in Table 2, we assigned all the peaks using 2D NMR analysis (COSY, HSQC, and HMBC) (see Supporting Information, Figure S2). All the peaks of free **HA** and **BA** in the mixture with **PPA** shifted to high frequency value in the ^{1}H NMR spectra. This might result from the interactions with **PPA** through hydrogen bonding. We propose their intermediate structures as **A** and **B** (Figure 3), in which the morpholine moiety is close to the phenyl ring of **PPA**, because NOE effect was observed between the phenyl protons of **PPA** and H_b of **HA** and **BA**.

(a) ^{1}H NMR



(b) ^{13}C NMR

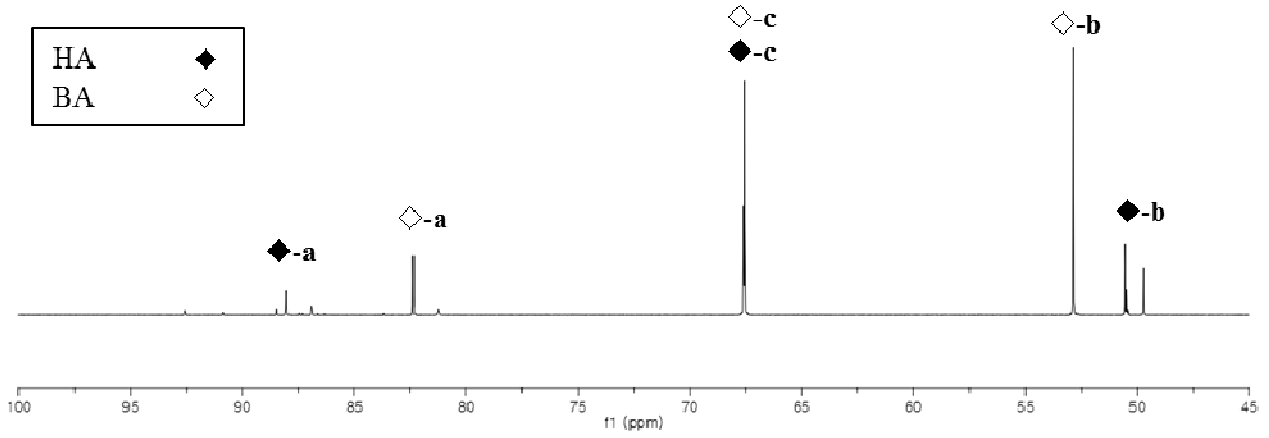


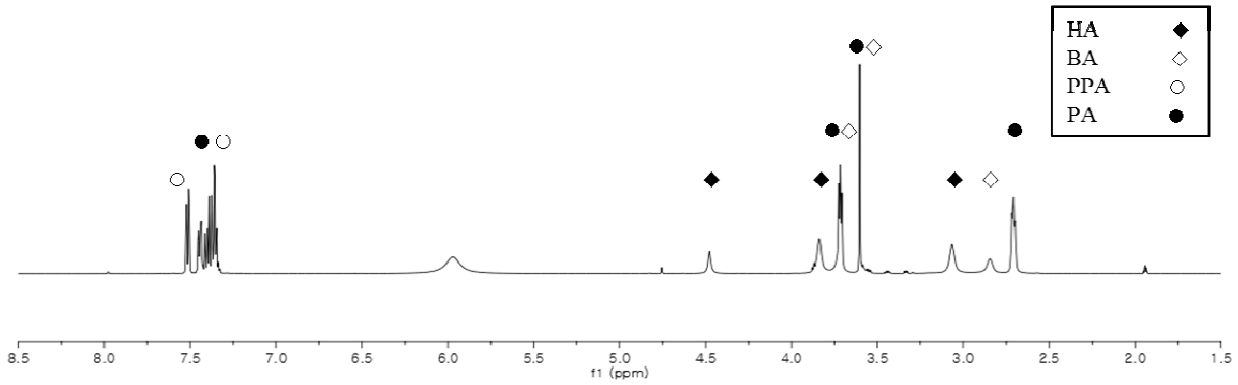
Figure 1. NMR spectra of **HA** and **BA** in CD_3CN.

Table 1. Assignment of ^{1}H and ^{13}C NMR of **HA** and **BA**[a]

Aminal[a]	^{1}H NMR (CD_3CN, ppm)	^{13}C NMR (CD_3CN, ppm)
HA	δ 4.09 (s, H_a), 3.59 (m, H_c), 2.60 (m, H_b), 2.26 (s, H_d)	δ 88.0 (C_a), 67.6 (C_c), 50.5 (C_b)
BA	δ 3.59 (m, H_c), 2.86 (s, H_a), 2.43 (t, H_b)	δ 82.4 (C_a), 67.6 (C_c), 52.8 (C_b)

[a] Reaction conditions: paraformaldehyde (9.0 mg, 0.3 mmol) and morpholine (26.1 mg, 0.3 mmol) were dissolved in CD_3CN (0.8 mL) and mixed for 2 h at 25 °C, and the resulting solution was monitored by NMR (500 MHz).

(a)^{1}H NMR



(b) ^{13}C NMR

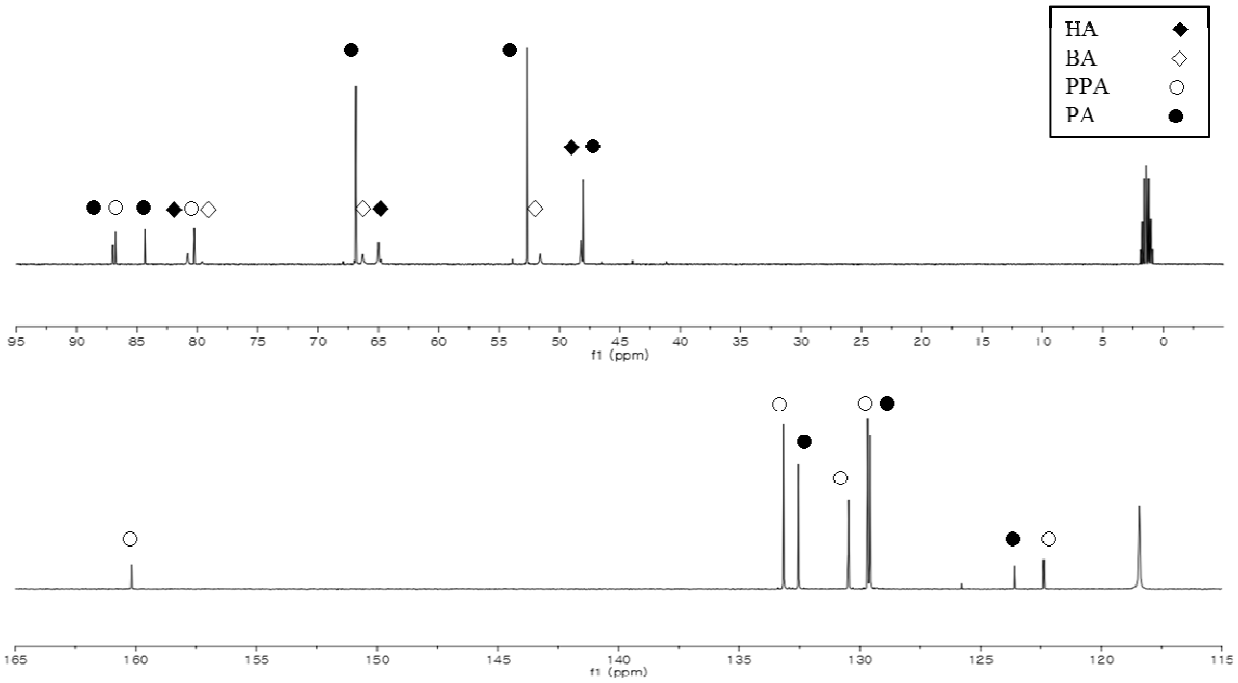
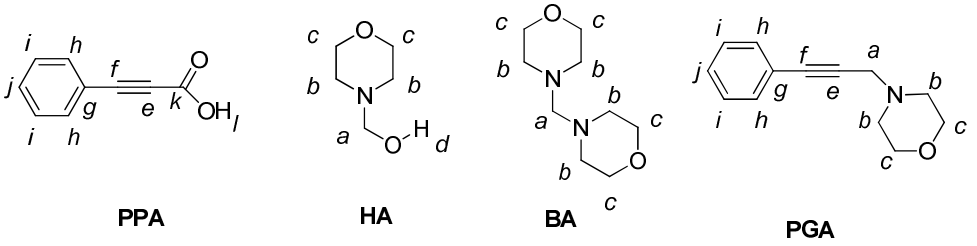


Figure 2. NMR spectra of the reaction mixture of **PPA**, paraformaldehyde and morpholine in CD_3CN.

Table 2. Characterization of all the reagents in the reaction mixture[a]



Compound	^{1}H NMR (CD_3CN, ppm)	^{13}C NMR (CD_3CN, ppm)
HA	δ 5.36 (br, H_d), 4.48 (s, H_a), 3.84 (t, H_c), 3.08 (t, H_b)	δ 80.8 (C_a), 65.0 (C_c), 48.2 (C_b)
BA	δ 3.74 (t, H_c), 3.65 (s, H_a), 2.47 (t, H_b)	δ 79.6 (C_a) 66.3 (C_c), 51.6 (C_b)
PPA	δ 7.52 (m, H_h) 7.42 (tt, H_j), 7.38 (m, H_i), 5.36 (br, H_l)	δ 160.2 (C_k) 133.2 (C_h) 130.5 (C_j), 129.7 (C_i), 122.4 (C_g) 87.0 (C_e), 80.2 (C_f)
PGA	δ 7.45 (m, H_h) 7.36 (m, H_i / H_j), δ 3.74 (t, H_c), 3.65 (s, H_a), 2.76 (t, H_b)	δ 132.6 (C_h) 129.7 (C_i), 129.6 (C_j), 123.6 (C_g), 87.0 (C_e), 84.3 (C_f), 66.9 (C_c), 52.7 (C_b), 48.0 (C_a)

[a] All the peaks were assigned based on the 2D NMR analysis

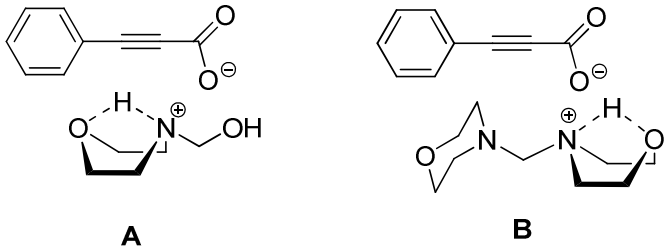


Figure 3. Proposed reaction intermediates **A** and **B**.

The adduct **HA**−**PPA** formed from **HA** and **PPA** was characterized in the DOSY (diffusion-ordered spectroscopy). DOSY, an NMR spectroscopic technique, is used to analyze the individual components of a chemical mixture without prior physical separation. High-resolution DOSY methods utilize the molecular diffusion property. In a typical two-dimensional DOSY spectrum of a complex mixture, the chemical shift is shown on one axis, and the diffusion coefficient is shown on the other axis for each component. Smaller molecules show higher diffusion coefficients. If the reaction intermediates are present before proceeding to the final product, then DOSY is the method of choice to observe such a fleeting state when it is not

possible, as in our case, to separate the reaction intermediates with chromatographic techniques such as HPLC.[50]

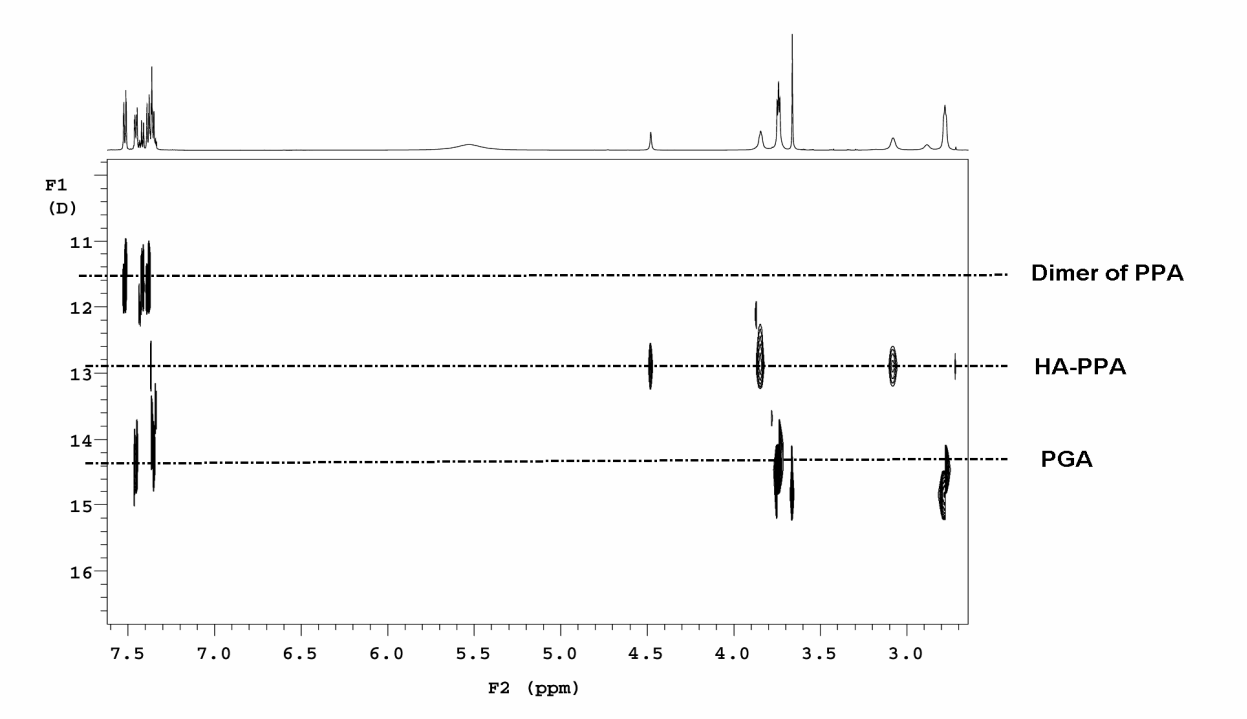


Figure 4. DOSY spectrum. DOSY analysis of a **HA**−**BA**−**PPA** mixture after 72 h of reaction at 65 °C in CD_3CN. Ordinate (F1 axis) represents the diffusion coefficient in 10^{10} m^2/s, and the other axis (F2 axis), abscissa, represents a regular one-dimensional ^1H NMR spectrum.

We were able to observe DOSY peaks, which can be attributed to the adducts of the starting materials, **HA** and **PPA** (denoted as **HA**−**PPA**, Figure 4). The three components of dimeric **PPA**, **HA**−**PPA** adduct, and **PGA** were observed in the order of diffusion coefficients according to the respective formula weights. The reaction intermediate, **HA**−**PPA**, is shown between the dimeric **PPA**, the largest formula weight compound with the lowest diffusion coefficient, and **PGA**, the smallest formula weight compound with a higher diffusion coefficient.

Moreover, the carbon peak of the carboxylic acid in free **PPA** shifted to high frequency value in the ^{13}C NMR when **PPA** was reacted with a mixture of paraformaldehyde and morpholine. As shown in Figure 5b, the carbonyl carbon of **PPA** was observed at δ 155.0 ppm; however, it appeared at δ 160.2 ppm in the reaction mixture. The alkynyl carbons shifted to low frequency value in the intermediate.

To follow the reaction profile, this reaction mixture was monitored at 65 °C by NMR. As shown in Figure 6, the integration values of proton peaks from **HA** and **BA** decreased, and those from product (**PGA**) increased with time. The proton peak of the carboxylic acid shifted to low frequency value, and its intensity decreased (see Supporting Information of Figure 3).

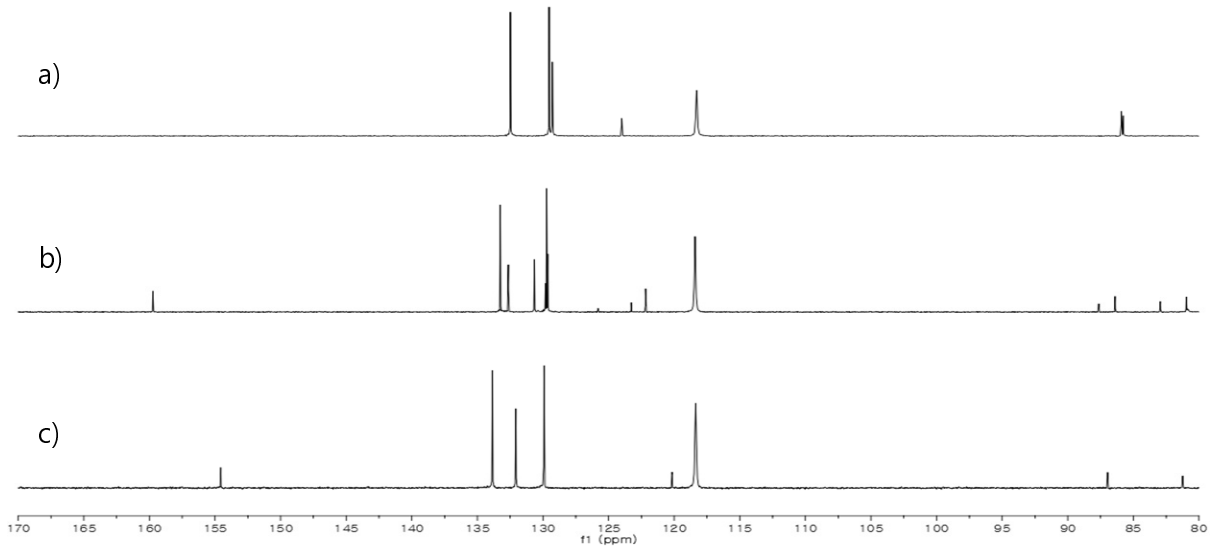


Figure 5. ^{13}C NMR data in CD_3CN. (a) **PGA**. (b) The reaction mixture of **PPA**, morpholine, and paraformaldehyde. (c) **PPA**.

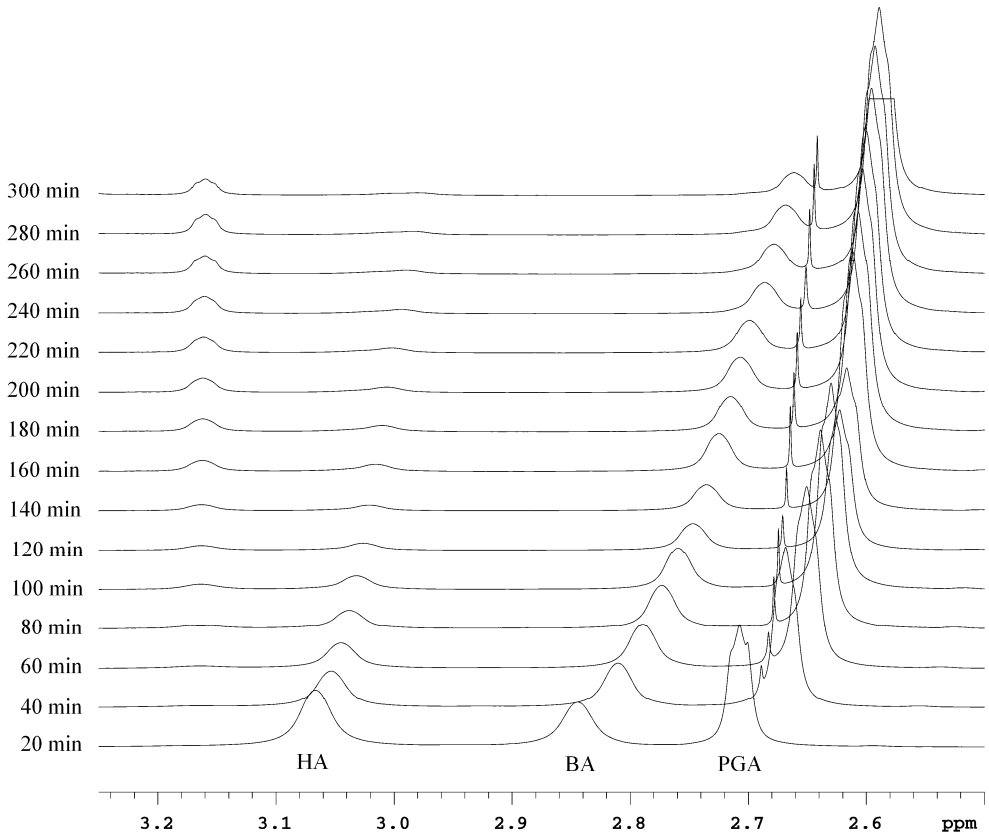


Figure 6. ^{1}H NMR data of the reaction mixture with **PPA**, paraformaldehyde and morpholine in CD_3CN.

Based on these spectroscopic data, the reaction profile was plotted as shown in Figure 7. The yields were determined using the internal standard tetramethylsilane. When **PPA** was added to a mixture of paraformaldehyde and morpholine, 40% of **PPA** was converted to the desired product in 10 min. As expected, the yield of propargylamine increased to 86% in 5 h; however, **PPA** was not completely consumed.

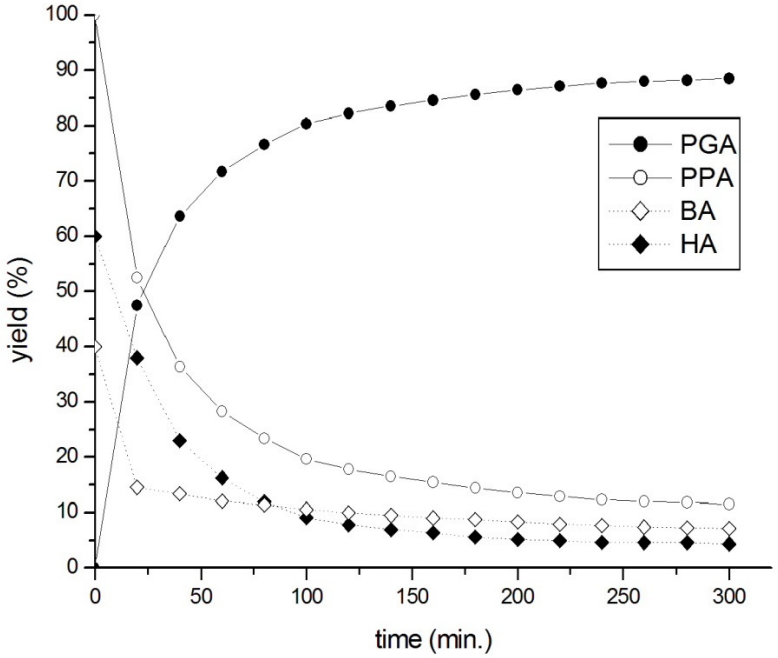
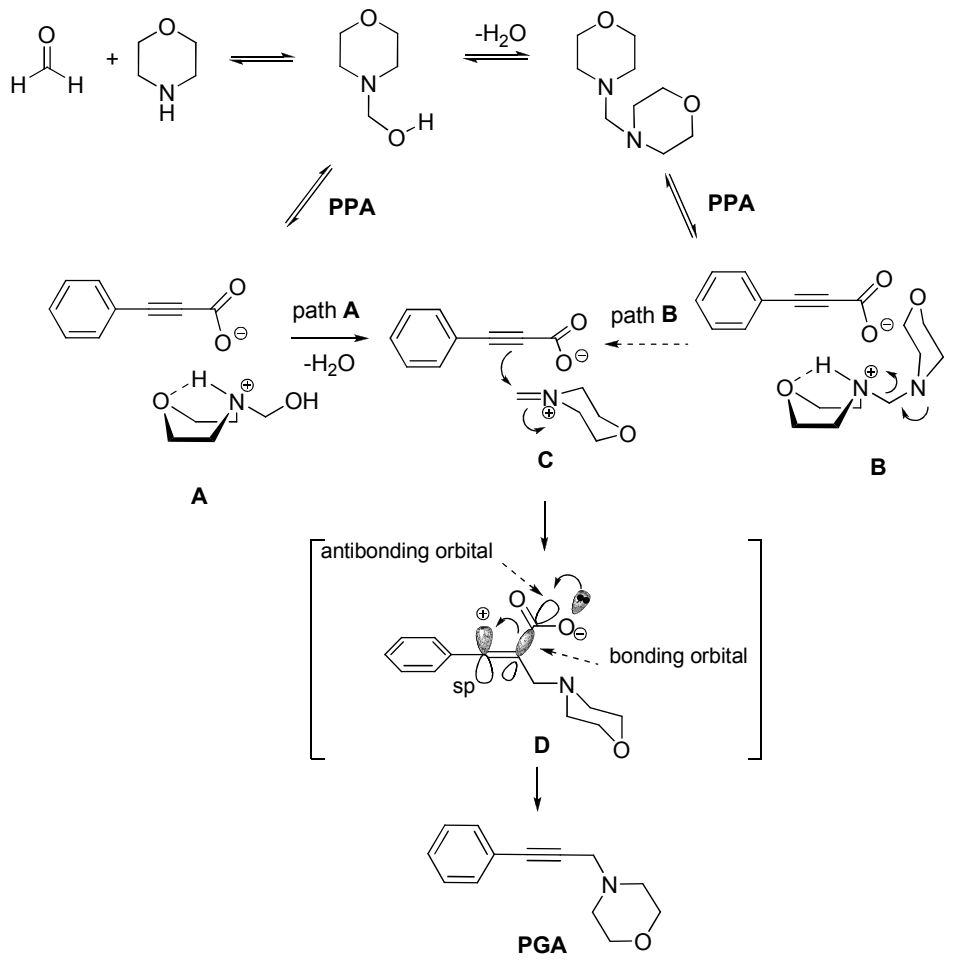


Figure 7. The reaction profile of the formation of **PGA** from **PPA** and paraformaldehyde and morpholine.

Based on these results, we proposed the reaction pathway as shown in Scheme 1. First, the reaction of paraformaldehyde and morpholine afforded the corresponding **HA** and **BA**. **HA** might be more reactive than **BA** in the decarboxylative coupling reaction. When the amount of morpholine was doubled, only **BA** was formed, and the desired product was obtained in a low yield (5%). However, the iminium ion C which is derived from the **HA** was not detected in the reaction mixture by $^{1}H–^{13}C$ HMBC 2D NMR analysis. The interaction of **HA** with **PPA** produced the hydrogen-bonding adduct **A** and provided the desired propargylamine through decarboxylation (path **A**). Path **A** is much favored than path **B**, because adduct **B** was not detected in NMR. Although vinyl carbocation intermediate **D** proposed in the previous report[47] was not detected in the reaction mixture by $^{1}H–^{13}C$ HMBC 2D NMR analysis, the NMR data analysis support that the decarboxylative coupling might proceed through the intermediate **A**. However, we do not rule out the possible pathway **B** in which the intermediate **B** reacts so fast.



Scheme 1. Proposed pathway of the formation of **PGA** from decarboxylative coupling reaction.

Conclusions

In summary, the reaction pathway of the decarboxylative coupling reaction of **PPA** with paraformaldehyde and morpholine was studied by NMR spectroscopic analysis. Two aminals (**HA** and **BA**) were formed in the reaction mixture, and **HA** showed higher reactivity than **BA**. Moreover, the interactions of these aminals with **PPA** formed the corresponding adducts, which were identified by 2D NMR analysis and DOSY. The decarboxylative coupling reaction of **HA** and **PPA** may be the major pathway in the formation of propargylamines.

Acknowledgements

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