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γ-Amino Butyric Acid (GABA) Synthesis Enabled by Copper-Catalyzed Carboamination of Alkenes

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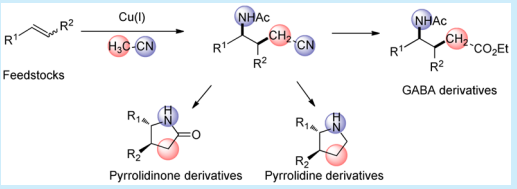
Supporting Information

ABSTRACT: γ-Amino butyric acid (GABA) is the chief inhibitory neurotransmitter in the mammalian central nervous system. Many GABA derivatives are used clinically to prevent or treat neurodegenerative diseases. Copper-catalyzed carboamination of alkenes offers an efficient method to fashion the core structure of GABA derivatives from alkenes. In this reaction, acetonitrile serves as the source of the carbon and nitrogen functionalities used to difunctionalize alkenes. Experimental and density functional theory (DFT) studies were carried out to investigate the mechanism of the reaction, and a copper-catalyzed radical-polar crossover mechanism is proposed.



Alkenes are readily available, and intermolecular carboamination of alkenes is a very effective strategy to construct C−C bonds and C−N bonds simultaneously.[1−4] Carboamination products of olefins include amines, amino acids, and other core structures present in natural products and pharmaceutically important chemicals. Despite the great synthetic potential of this strategy, the successful carboamination of olefins mainly focused on the reaction with intramolecular carbon sources,[1] nitrogen sources,[2] or both carbon and nitrogen sources.[3] The carboamination of olefins with both intermolecular carbon and nitrogen sources[4] is still difficult and has rarely been explored.

γ-Amino butyric acid (GABA) is a significant inhibitory neurotransmitter in the mammalian central nervous system.[5] Many GABA derivatives capable of crossing the blood−brain barrier are used clinically to prevent or treat neurodegenerative diseases.[6] A convenient synthesis of structurally diverse compounds containing the GABA moiety could facilitate the drug development process. Substituted pyrrolidines and pyrrolidinone derivatives are extremely common core structures of biologically active molecules and ligands.[7] Despite the numerous methods developed for the synthesis of substituted pyrrolidine and pyrrolidinones, synthesis of these structures, especially 2,3-*trans*-disubstuted pyrrolidines and pyrrolidinones from alkenes, has been reported infrequently.[8]

Nitriles are inexpensive chemicals, widely used as solvents in organic reactions. Recently, they have been used elegantly by Zhu et al.[9] and other groups[10] in the functionalization of alkenes. Very recently, Li et al. developed an efficient 1,2-carboamination of alkenes with alkyl nitriles as carbon functionality.[4k] It would be interesting if nitriles could serve as the source of carbon and nitrogen functionalities in the difunctionalization of alkenes. We have developed a series of alkylation reactions via a radical pathway,[11] and here, we report our continuing efforts to achieve the carboamination of alkenes with nitriles as both carbon and nitrogen functionalities to afford GABA analogues, substituted pyrrolidines and pyrrolidinones (Figure 1).

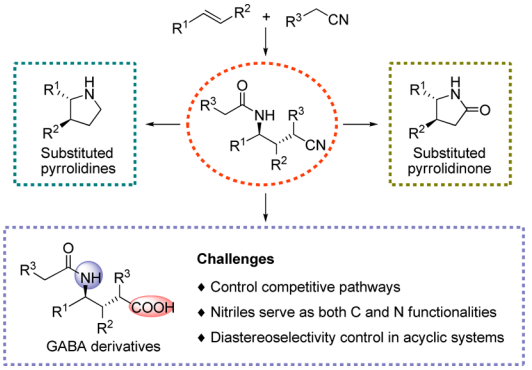


Figure 1. Carboamination of alkenes to GABA derivatives.

We began this study by seeking an appropriate radical precursor, which is reactive enough to abstract a hydrogen atom from the nitrile to initiate the radical relay process. The radical precursor should not be too reactive, or it could add to the alkene and produce undesired compounds. Radical precursors (**1a**−**1g**) were screened using the model reaction depicted in Scheme 1, but unfortunately, none of these reactions yielded the desired product (**4a**). In the case of the phenyl radical

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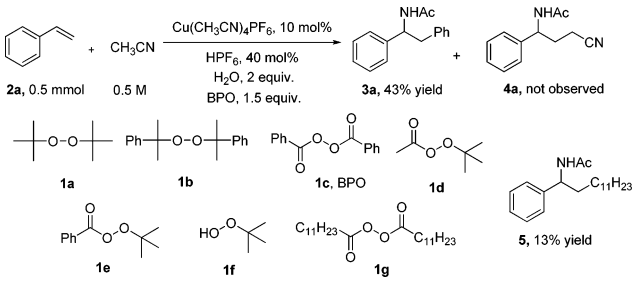
Scheme 1. Initial Studies for Carboamination of Styrene

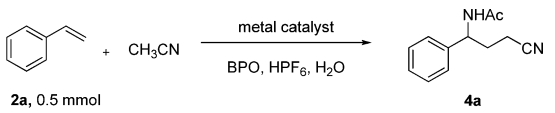


precursor (**1c**, BPO) and alkyl radical precursor (**1g**, LPO), **3a** and **5** were isolated in 43% and 13% yield, respectively.

A computational DFT study was performed to evaluate the competitive radical additions and seek a possible mechanism leading to the desired product (**4a**). The overall potential energy surface and the critical competitive steps are depicted in Figures S2 and S3. The difference in the calculated activation free energy ($\Delta G^{\ddagger}$) between **A-TS2** and **B-TS2** is 3.4 kcal/mol. According to the Boltzmann distribution, the addition of the phenyl radical to styrene is about 300 times faster than hydrogen abstraction from acetonitrile which generates a $\cdot CH_2CN$ radical. This free energy difference suggests that it may be possible to control the outcome of the competitive pathways by regulating concentrations of CH_3CN and styrene.[12]

As suggested by these DFT calculations, we reoptimized the reaction conditions and used a larger volume of CH_3CN (Table 1). When the quantity of CH_3CN was increased from 2 to 8 mL, the desired product **4a** was obtained in 40% yield. Encouraged by this result, we further increased the amount of CH_3CN to 20 mL and found that **4a** could be isolated from this reaction in 68% yield. Other catalysts such as $Fe(OTf)_3$, $Pd(OAc)_2$, $NiBr_2$, and $CoCl_2$ were examined under these conditions, but no desired product was formed. When BPO was added into the reaction solution in three portions, the yield was improved to 73%. Further screening of copper catalysts showed that CuI was the optimum catalyst, delivering a yield of 79%.

Table 1. Reaction Condition Optimizations[a]



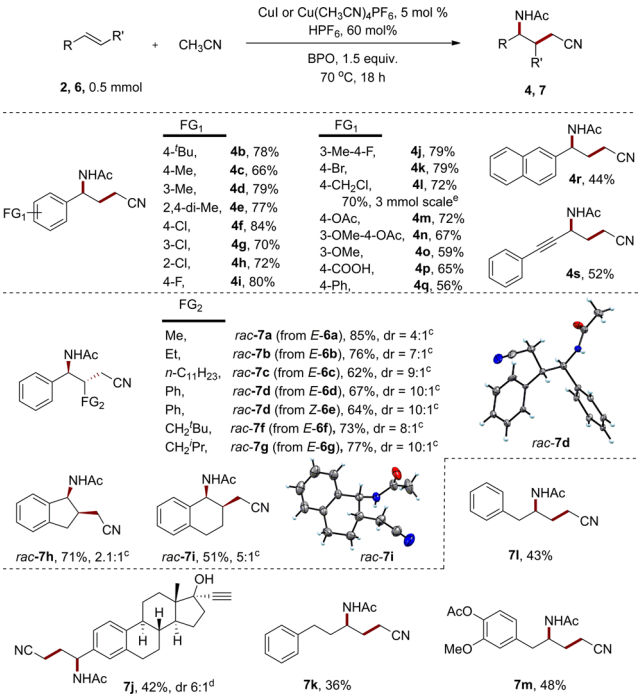
entry	metal/mol %	solvent/mL	acid (equiv)	BPO (equiv)	yield (%)[b]
1	$Cu(CH_3CN)_4PF_6$/5	2	HPF_6 (0.4)	1.25	0
2	$Cu(CH_3CN)_4PF_6$/5	8	HPF_6 (0.4)	1.25	40
3	$Cu(CH_3CN)_4PF_6$/5	20	HPF_6 (0.4)	1.25	68
4	$Fe(OTf)_3$/10	20	HPF_6 (0.4)	1.25	ND
5	$Pd(OAc)_2$/10	20	HPF_6 (0.4)	1.25	ND
6	$NiBr_2$/10	20	HPF_6 (0.4)	1.25	ND
7	$CoCl_2$/10	20	HPF_6 (0.4)	1.25	ND
8	$Cu(CH_3CN)_4PF_6$/5	20	HPF_6 (0.4)	1.25[d]	73
9	CuI/5	20	HPF_6 (0.4)	1.25[d]	79
10	CuI/5	30	HPF_6 (0.4)	1.25[d]	85
11	CuI/5	30	HPF_6 (0.6)	1.5[d]	88
12[e]	CuI/5	30	HPF_6 (0.6)	1.5[d]	88 (84)[c]

[a]Reactions were conducted with styrene (0.5 mmol), BPO and CH_3CN, H_2O (2 equiv), 70 °C for 18 h. [b]Yield of product detected by GC. [c]Yield of isolated product in parentheses. [d]BPO was added in three portions at intervals of 2 h. [e]Without adding H_2O.

Optimization of the amounts of solvent and acid showed that the most effective conditions afforded the product in 88% yield. No desired product was observed in the absence of copper catalyst, and acid screening revealed that HPF_6 was necessary for the reaction, while other acids failed to improve the reaction further (see details in Table S1).

With the optimal conditions in hand, the generality of this strategy with respect to different alkene substrates was examined (Table 2). Reactions of terminal vinylarenes afforded the corresponding product (**4b**–**4r**) in 44–84% yields. Styrenes with various substituents, such as ^{t}Bu, Me, halogens, OAc, and COOH, were tolerated in this reaction. Reaction of the enyne delivered the target product **4s** in 52% yield. Remarkably, when 1,2-disubstituted olefins were served as the suitable substrates in this reaction (**6a**–**6g**), the diastereoisomer ratios range from 4:1 to 10:1 in the presence of conc. H_2SO_4 as an additive.[13] For the cyclic olefins, the yields were moderate although the dr values were low. Reactions of unconjugated olefins afforded the corresponding products (**7k**–**7m**) in 36–48% yields, along with Heck-type byproducts. Unfortunately, only a trace amount of the desired product was detected with 4-isopropenyltoluene as the reaction substrate.[41]

Table 2. Copper-Catalyzed Carboamination of Alkenes[a,b]



[a]Reaction conditions: alkene (0.5 mmol), BPO (1.5 equiv), and CH_3CN (30 mL). BPO was added in three portions at intervals of 2 h. [b]Yields of isolated products. [c]1 equiv of H_2SO_4 was added as an additive. [d]H_2O (2.0 equiv), HPF_6 (0.2 equiv). [e]The yield of scale-up reaction: alkene (3 mmol) and CH_3CN (130 mL).

Next, mechanistic studies were conducted in an effort to understand the details of the competitive pathways. Radical trapping and isotope labeling experiments shown in Scheme 2 were carried out to probe the fate of the phenyl and α-cyanoalkyl radicals. Upon addition of TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] to the reaction, compounds **9** and **10** were detected by GC-MS (see Supporting Information (SI)), implying the existence of both α-cyanoalkyl and benzylic radicals. When CD_3CN was used as the solvent, deuterated

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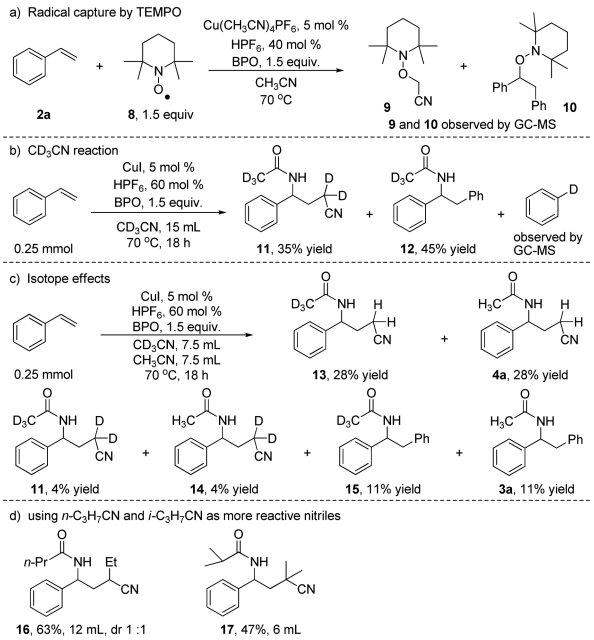
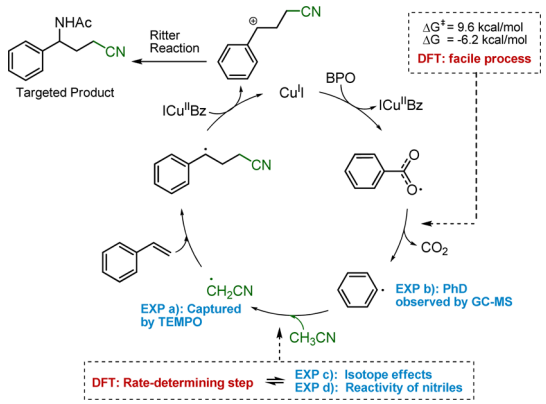
Scheme 2. Experimental Mechanistic Studies



benzene was formed, indicating that the phenyl radical was indeed able to abstract an H(D) atom from acetonitrile. Next, intermolecular competition between CD_3CN and CH_3CN was carried out. The product ((**13** + **4a**)/(**11** + **14**)) ratio of the reaction in a 1:1 mixed solvent is approximately 7:1, implying that the formation of the α-cyanoalkyl radical is irreversible.[14] Similar yields for the couples **13**/**4a**, **11**/**14**, and **15**/**3a** suggest that no isotope effect could be found in the Ritter reaction step. According to DFT calculations, butyronitrile and isobutyronitrile are expected to be more susceptible to H-abstraction to form radicals (Figure S4). These two nitriles were examined under similar reaction conditions, and it was found that with a smaller volume of nitrile, products **16** and **17** were obtained in 63% and 47% yield, respectively.

A radical-polar crossover mechanism for the reaction is proposed in Scheme 3.[15] The $Cu^{(I)}$ complex transfers an electron to BPO to form the $Cu^{(II)}$ compound and a phenyl acyloxy radical. Subsequent decarboxylation affords a phenyl radical. This phenyl radical further abstracts hydrogen from acetonitrile and generates an α-cyanoalkyl radical which reacts with styrene to form the benzylic radical. The benzylic radical is

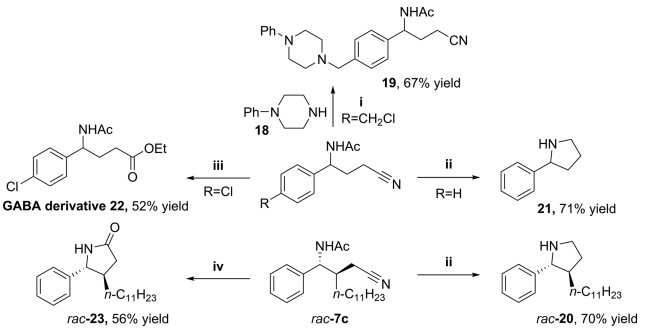
Scheme 3. Proposed Catalytic Cycle



oxidized by $Cu^{(II)}$ to a carbocation which undergoes a Ritter reaction in the presence of acid, delivering the desired product.[16] These steps are supported by our DFT calculations (Figure S3) and mechanistic experiments (Scheme 2). The oxidation of $Cu^{(I)}$ to $Cu^{(III)}$ by BPO is an alternative pathway.[4b]

To explore the synthetic potential of this method, transformations of various products were carried out as shown in Scheme 4. The product **4l** was readily transformed to **19**, an

Scheme 4. Synthetic Applications of Carboamination Reactions[a]



[a]Reagents and conditions: (i) Cs_2CO_3, CH_3CN, rt, 16 h; (ii) Na, *n*-BuOH, 120 °C, 2 h; (iii) EtOH, Conc. HCl, 80 °C, 8 h; (iv) EtOH, Conc. HCl, H_2SO_4 (30%), 100 °C, 10 h. See details in SI.

analogue of a bioactive molecule.[17] Next, products **7c** and **4a** were converted to the 2,3-*trans*-disubstituted pyrrolidine **20** and 2-substituted pyrrolidine **21**. This type of reaction is unprecedented. Furthermore, the protected γ-amino acid (**22**) was synthesized from **4f** in 52% yield. Significantly, the carboamination products can be converted to analogues of racetam family drug molecules.[18] As an example of this type of transformation, compound **23** was synthesized from **7c**.

In summary, we have developed a copper-catalyzed carboamination reaction of alkenes which offers an efficient pathway to construct the core structure of GABA derivatives from alkenes. Nitriles serve as the source of carbon and nitrogen functionalities and difunctionalize the alkenes. Experimental studies and DFT calculations were carried out to probe the mechanism, and a copper-catalyzed radical-polar crossover mechanism is proposed. Analogues of drug molecules and other useful compounds were synthesized from the carboamination products and exemplify the potential value of this method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01969.

Experimental details, data, and spectra (PDF)
Crystallographic data (CIF, CIF)

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Notes

The authors declare no competing financial interest.

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