Radical Carbonylation

Alkyne Carbonylation by Radicals: Tin-Radical-Catalyzed Synthesis of α-Methylene Amides from 1-Alkynes, Carbon Monoxide, and Amines**

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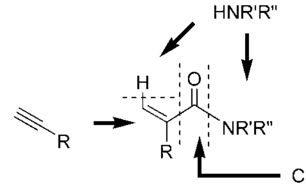
Radical reactions have become an important tool in organic synthesis.[1] Radical carbonylation is a useful method for the preparation of a variety of carbonyl compounds.[2] We previously reported that acyl-radical cyclization onto an imine nitrogen atom provides a useful route to lactam rings.[3] We also recently found that intramolecular trapping of an α-ketenyl radical by an amino group leads to the formation of cyclic amides.[4] Acrylamides and derivatives thereof are employed in a wide range of organic reactions, which include nucleophilic additions, cycloaddition reactions, and radical reactions, to name just a few.[5] They are also extensively used in the synthesis of polymeric materials.[6] The goal of this work was to develop a novel synthesis of acrylamide derivatives by taking advantage of a hybrid radical/ionic reaction involving the radical carbonylation of alkynes and subsequent ionic trapping of the resulting carbonyl-containing radical species by amines (Scheme 1).[7,8]



Scheme 1. A convergent synthesis of 2-substituted acrylamides.

Thus, when 1-octyne was treated with propylamine (50 mol equiv) and pressurized CO (85 atm) in the presence of 30 mol% tributyltin hydride and 20 mol% 2,2′-azobisisobutyronitrile (AIBN), the reaction proceeded smoothly [Eq. (1)]. *N*-Propyl-2-hexylacrylamide (**3a**) was obtained in 82% yield after isolation by flash chromatography on silica gel with EtOAc as eluent. α-Stannylmethylene amide **4a**

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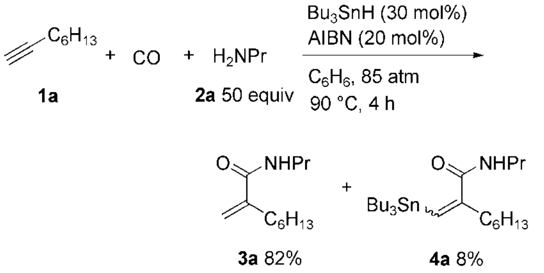
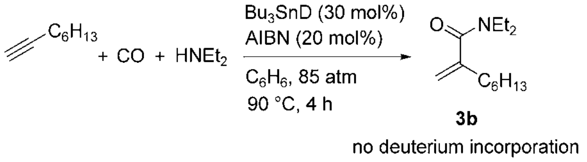
(8%), formed as a byproduct, can be converted to **3a** by protodestannylation with MeOH and Me_3SiCl (room temperature, 10 min). The amount of tributyltin hydride can be reduced to 20 mol%, which gave 75% yield of **3a**, whereas with 10 mol% of tributyltin hydride chain propagation is not so sufficient and the yield of **3a** decreased to 49%. We also tested PhSH instead of Bu_3SnH, but the reaction gave a complex mixture containing **3a** in only low yield.



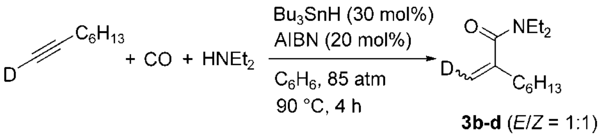
(1)

A variety of primary and secondary amines were examined for use in this reaction, and all proved to work well (Table 1). Terminal alkynes with hydroxy, chloro, phenylsulfide, acetoxy, and benzyloxy functionalities can be efficiently carbonylated to give the corresponding α-methylene amides in good to excellent yields (entries 3–9). The carbonylation of phenylacetylene (**1i**) in the presence of pyrrolidine gave the corresponding amide **3j**, albeit in rather modest yield (entry 10). In the case of substrate **1j** with two alkynyl moieties, the reaction proceeded chemoselectively on the terminal alkyne to provide the corresponding amide **3k** (entry 11).

To obtain some insight into the reaction mechanism, we conducted labeling experiments with tributyltin deuteride [Eq. (2)] and 1-deuterated 1-octyne [Eq. (3)]. Deuterium incorporation was not observed in the first case, but it was detected in the second case, which is consistent with a scenario in which an amine hydrogen atom is transferred to the vinylic position of the product.



(2)

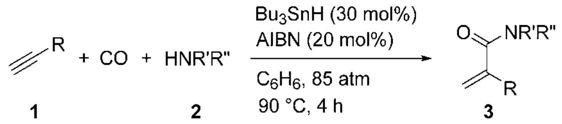


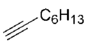
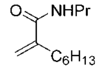
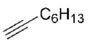
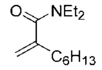
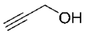
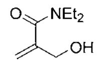
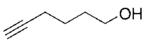
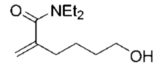
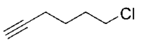
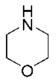
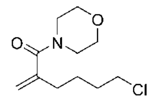
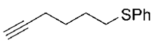
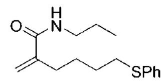
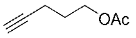
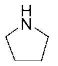
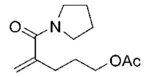
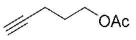
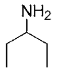
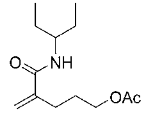
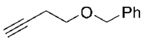
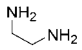
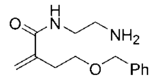
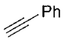
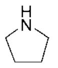
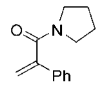
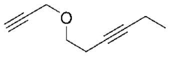
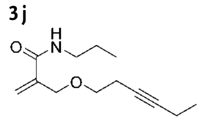
(3)

A tin-radical-catalyzed hybrid radical/ionic mechanism is proposed in Scheme 2. Addition of tributyltin radical to the alkyne terminus generates a vinyl radical, which then undergoes carbonylation to generate an α-ketenyl radical. Intermolecular trapping of the α-ketenyl radical by amines affords 1-hydroxyallyl radicals. A subsequent 1,4-H migration[9] to give α-keto radical followed by β-fission leads to the formation of α-methylene amides and regenerates tributyltin radical.[10]

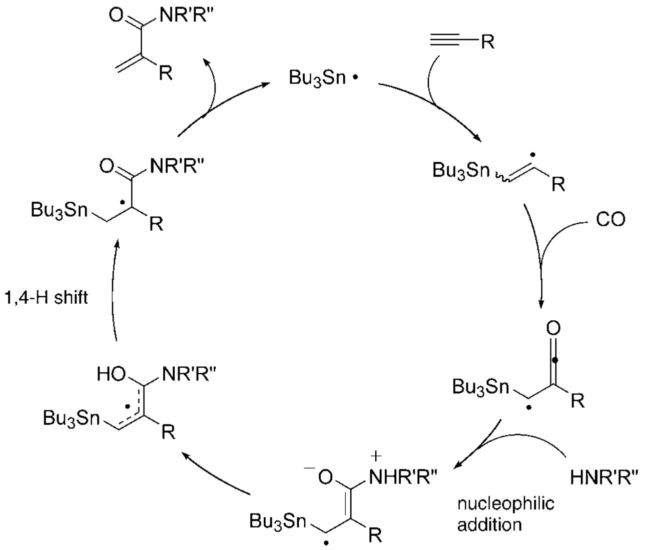
To obtain further insight into the unusual radical 1,4-H shift, DFT calculations were carried out for the isomerization

Table 1: Synthesis of α-methylene amides by tin-radical-catalyzed carbonylation of 1-alkynes.[a,b]



Entry	Alkyne	Amine	Product	Yield [%][c]
1	 **1a**	H_2NPr **2a**	 **3a**	82
2	 **1a**	$HNEt_2$ **2b**	 **3b**	75
3	 **1b**	$HNEt_2$ **2b**	 **3c**	74
4	 **1c**	$HNEt_2$ **2b**	 **3d**	76
5	 **1d**	 **2c**	 **3e**	69
6	 **1e**	H_2NPr **2a**	 **3f**	82
7	 **1f**	 **2d**	 **3g**	92
8	 **1g**	 **2e**	 **3h**	69
9	 **1h**	 **2f**	 **3i**	89
10	 **1i**	 **2d**	 **3j**	56
11	 **1j**	H_2NPr **2a**	 **3k**	63

[a] Alkyne **1** (1 mmol), amine **2** (50 mmol), Bu_3SnH (0.3 mmol), AIBN (0.2 mmol), CO (85 atm), benzene (20 mL), 90°C, 4 h. [b] Generally, less than 10% of the α-stannylmethylene amide **4** was formed as by-product. [c] Yields after isolation by flash chromatography on SiO_2.



Scheme 2. A hybrid radical/ionic mechanism for tin-catalyzed carbonylation of alkynes leading to 2-substituted acrylamides.

of a 1-hydroxyallyl radical ($HO(H_2N)C{=}CCH(\cdot)SnH_3$) to the corresponding enol radical ($H_2NC{=}OCH(\cdot)CH_2SnH_3$).[11] As shown in Figure 1, the 1,4-H migration is predicted to be exothermic by 80.0 $kJ\,mol^{-1}$, and the reaction via a five-membered cyclic transition state is a possible reaction pathway for the proposed 1,4-H shift.

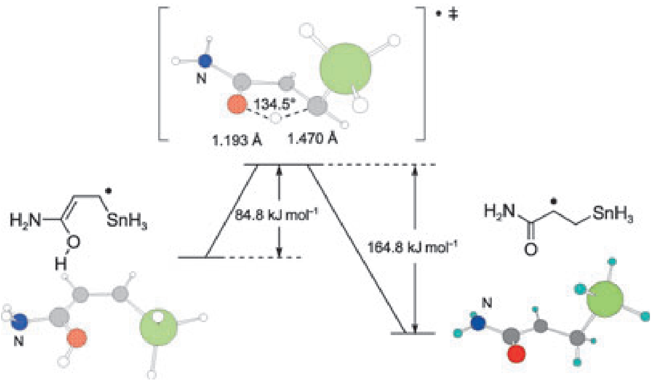


Figure 1. Optimized structures and energy barriers for the 1,4-H shift calculated at the CCSD(T)/DZP//BHLYP/DZP level of theory.

In summary, we have reported a new method for the carbonylation of alkynes, which is unique in being catalyzed by tributyltin radicals. Ionic trapping of the α-ketenyl radical by amines and radical 1,4-H shift from the resulting 1-hydroxyallyl radical are the keys to the success of the reaction. Thus, the radical/polar crossover process provides a new route for the carbonylation of alkynes without the use of transition-metal catalysis.

Experimental Section

AIBN (33.9 mg, 0.21 mmol), benzene (20 mL), 1-octyne (**1a**, 113.6 mg, 1.03 mmol), propylamine (**2a**, 4.1 mL, 50 mmol), and Bu_3SnH (82.6 mg, 0.28 mmol) were placed in a 50-mL stainless steel autoclave. The autoclave was closed, purged three times with carbon monoxide, pressurized with 85 atm of CO, and then heated at 90°C for 4 h. Excess CO was discharged at room temperature. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient from hexane to hexane/EtOAc 2:1) to give **3a** (169.9 mg, 82%), (*E*)-**4a** (28.4 mg, 6%), and (*Z*)-**4a** (10.8 mg, 2%).

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[10] As for the formation of tin-containing by-product **4a**, hydrogen abstraction from 1-hydroxyallyl radical may be a possible reaction course. For a recent mechanistic study on a related system, see A. L. J. Beckwith, V. W. Bowry, W. R. Bowman, E.

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