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Visible Light-Induced Iodine-Catalyzed Transformation of Terminal Alkynes to Primary Amides *via* C≡C Bond Cleavage under Aqueous Conditions

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Abstract: The visible light-induced iodine-catalyzed oxidative cleavage of the C≡C bond for transforming terminal alkynes into primary amides in the presence of ammonia under aqueous conditions is described. This metal-free protocol which ensued *via* initial hydroamination of the acetylene bond followed by liberation of diiodomethane (CH_2I_2) was found to be applicable to aromatic, heteroaromatic and aliphatic alkynes.

Keywords: alkynes; amides; cleavage reaction; hydroamination; hydrogen peroxide; iodine

Amongst many reactions of the C≡C bond,[1] its cleavage is considered to be one of the most challenging targets.[2,3] Earlier C≡C bond cleavage methodologies often required stoichiometric amounts of organometallic reagents and oxidants,[4] but transition metal-catalyzed activation of the C≡C bond under oxidative conditions has led to various methods to produce acids, esters and nitriles.[5] Nonetheless, harsh reaction conditions and use of rare and/or toxic metal complexes in these methods underscore the need to develop metal-free approaches to C≡C bond cleavage. Although by using stoichiometric amounts of different oxidizing agents, alkynes were recently shown to be viable precursors to acids, nitriles, esters and secondary or tertiary amides (Figure 1),[6–10] we noticed a lack of any report for the direct conversion of terminal alkynes to primary amides. Owing to the ubiquity of the amide bond in biological systems, functional materials and pharmaceuticals, development of complementary approaches for constructing it is of profound interest.[11] In this context, during our work on the development of iodine-mediated cascade reactions,[12] we envisaged that addition of iodine to a ter-

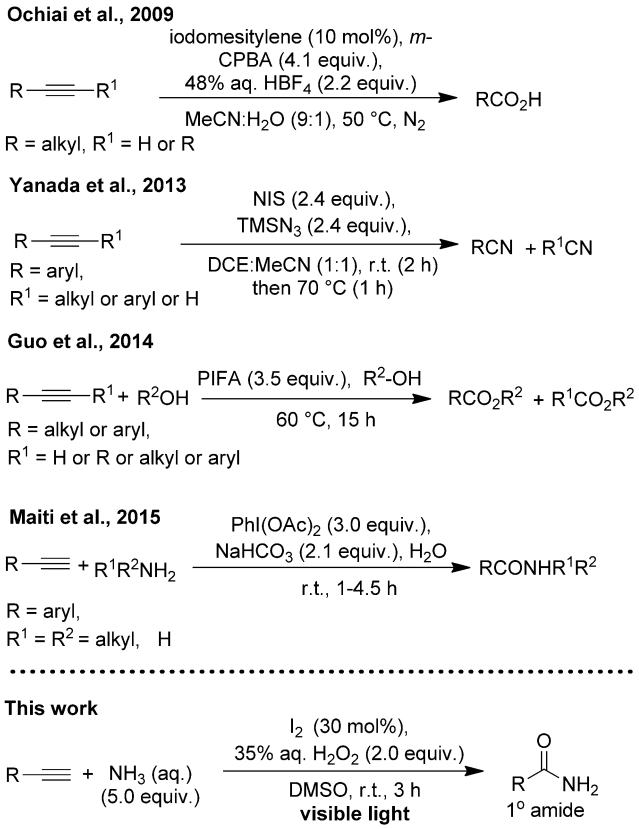


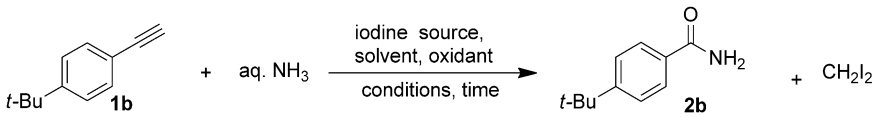
Figure 1. Metal-free approaches for the cleavage of C≡C bond.

minal alkyne would generate an iodonium cation which may undergo a nucleophilic attack of ammonia according to Markovnikov's rule followed by hydrolysis to produce a primary amide (*vide infra*). Our hypothesis relied on the reports wherein (i) terminal alkynes gave ketones *via* hydration,[13] (ii) acetophenones afforded benzamides in the presence of iodine and aqueous ammonia[14] and (iii) reaction of terminal alkynes with molecular iodine under oxidative conditions produced diiodoalkenes or α,α-diiodo ketones.[15,16] Working towards this objective, we now report an iodine-catalyzed transformation of terminal alkynes to primary amides in the presence of visible light.

Initially we investigated the iodine-catalyzed cleavage reaction of 1-(*tert*-butyl)-4-ethynylbenzene (**1b**) with 5.0 equiv. of ammonia (25% aqueous) in the presence of molecular iodine (1 equiv.) in DMSO at room temperature as a model for optimizing the conditions where the amide **2b** was obtained in 38% yield along with other side products (Table 1). Performing the reaction at 90 °C improved the yield of **2b** to 46% while replacing molecular iodine with NIS as the iodine source reduced the yield of **2b** to only 26%. We then screened the reaction in the presence of external oxidants including TBHP, H_2O_2, $K_2S_2O_8$, oxone and molecular oxygen and discovered that in each case the reaction was completed in 8 h and yields of the product were better, although aqueous H_2O_2 (2.0 equiv.) was superior. During purification by column chromatography, we isolated a highly nonpolar compound in a minor quantity which was characterized as diiodomethane (CH_2I_2). It is widely known that CH_2I_2 liberates iodine in the presence of light and therefore next we performed the reaction of **1b** and aqueous ammonia in the presence of iodine and H_2O_2 under visible light at room temperature when, to our delight, the reaction was completed in 3 h to afford **2b** in 88% yield. Subsequently we discovered that reducing the amount of iodine to 30 mol% furnished the product in 92% yield and completion of the reaction was evident for the naked eye. Further reduction of iodine to 20 mol% though afforded **2b** in 90% yield, but prolonged the reaction time to 8 h. Replacing DMSO with DMF reduced the yield of **2b** to 62% whereas the reaction failed when water was used as the medium. Finally, the absence of an external oxidant was found to decrease the yield of **2b** to 52% with increased completion time. Thus the optimal conditions were identified as terminal alkyne (1.0 equiv.), ammonia (25% aqueous, 5.0 equiv.), iodine (30 mol%), H_2O_2 (2.0 equiv.) in DMSO at room temperature under visible light for 3 h.

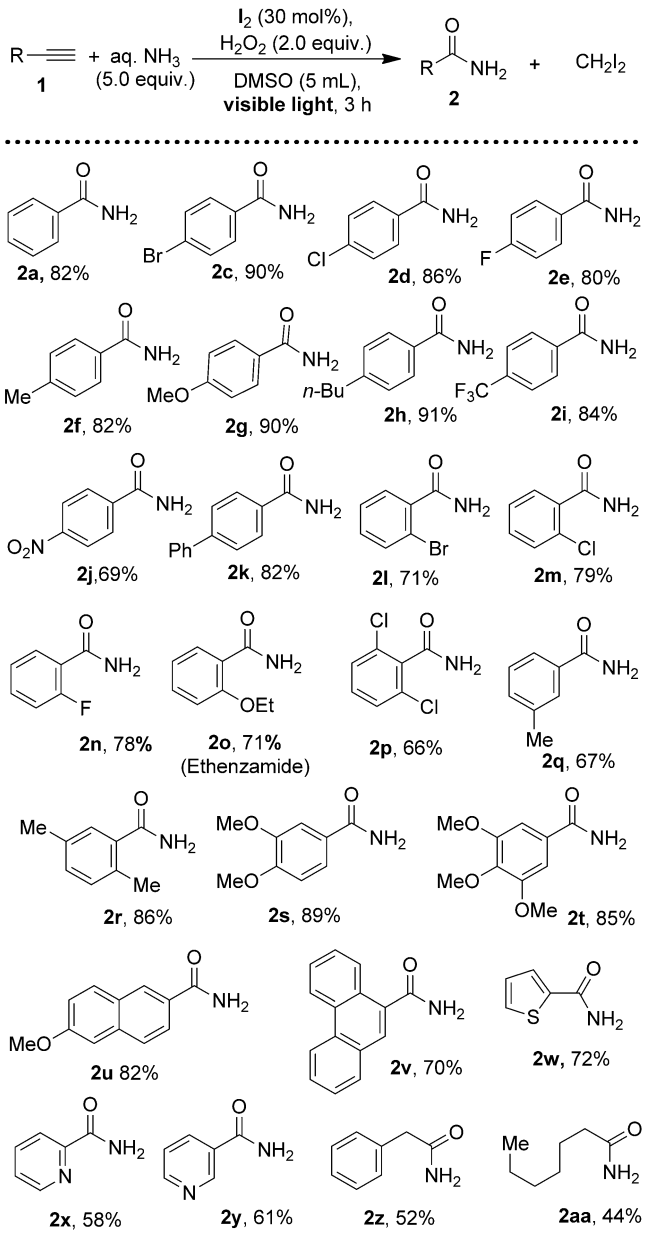
We next worked upon expanding the scope of the reaction by including a broad range of alkynes as delineated in Scheme 1. The alkynes used for the study were either commercially procured or were prepared using reported procedures.[17] In a first set of reactions several substituted ethynylbenzenes (**1a–1t**) bearing substituents with different electronic properties were examined and it was found that in all cases the respective benzamides (**2a–2t**) were isolated in excellent yields. It was gratifying to note that the amide **2o** also

Table 1. Optimization of the reaction conditions for transforming alkynes to primary amides *via* C≡C bond cleavage.[a]



Entry	Reagent (equiv.)	Solvent	Oxidant (equiv.)	Temperature	Time [h]	Yield [%][b]
1	I_2 (1.0)	DMSO	–	r.t.	12	38
2	I_2 (1.0)	DMSO	–	90 °C	12	46
3	NIS (1.0)	DMSO	–	90 °C	12	26
4	I_2 (1.0)	DMSO	TBHP (2.0)	90 °C	8	68
5	I_2 (1.0)	DMSO	H_2O_2 (2.0)	90 °C	8	86
6	I_2 (1.0)	DMSO	$K_2S_2O_8$	90 °C	8	78
7	I_2 (1.0)	DMSO	Oxone	90 °C	8	52
8	I_2 (1.0)	DMSO	O_2	90 °C	8	54
9	I_2 (1.0)	DMSO	H_2O_2 (2.0)	light (r.t.)	3	88
10	**I_2 (0.3)**	**DMSO**	**H_2O_2 (2.0)**	**light (r.t.)**	**3**	**92**
11	I_2 (0.2)	DMSO	H_2O_2 (2.0)	light (r.t.)	8	90
12	I_2 (0.3)	DMF	H_2O_2 (2.0)	light (r.t.)	3	62
13	I_2 (0.3)	H_2O	H_2O_2 (2.0)	light (r.t.)	3	–
14	I_2 (0.3)	DMSO	–	light (r.t.)	8	52

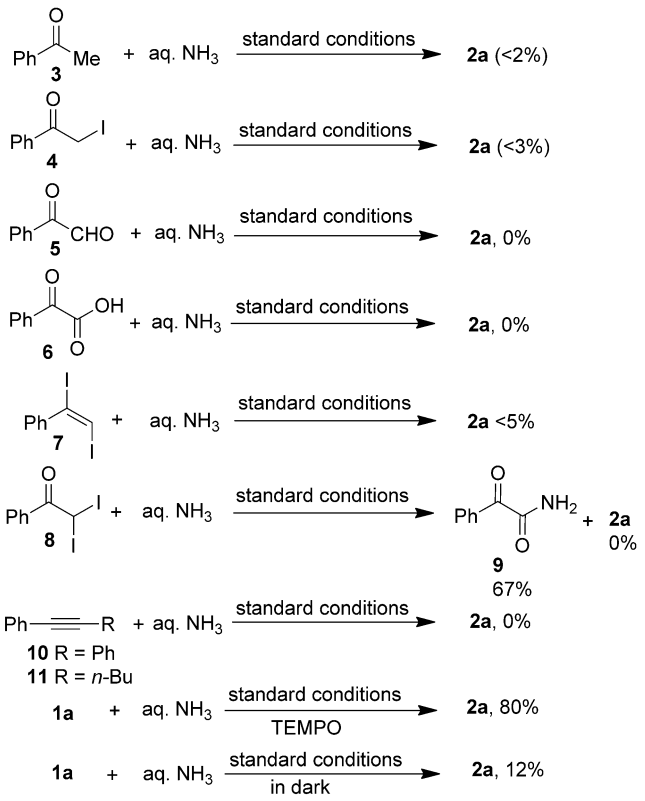
[a] All reactions were carried out using **1b** (0.2 g, 1.26 mmol), aqueous NH_3 (25%) 0.107 mL (6.3 mmol), DMSO (5 mL).
[b] Isolated yields after column chromatography.



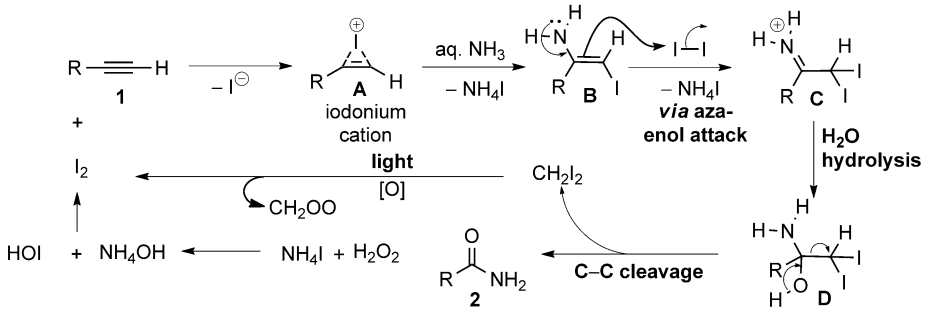
Scheme 1. Scope of the protocol for the transformation of terminal alkynes (**1**) to primary amides (**2**). All reactions were performed with 0.2 g of alkyne **1** and isolated yields of **2** after column chromatography are given.

known as Ethenzamide, an analgesic and anti-inflammatory agent, was obtained in 71% yield whereas **2s** and **2t**, the precursors for drugs Itopride and Trimethobenzamide were isolated in 89% and 85% yields, respectively. Even the naphthalene- and anthracene-based alkynes (**1u** and **1v**) furnished the corresponding amides **2u** and **2v** in 70–82% yields. Subsequently, heterocyclic alkynes (**1w–1y**) and aliphatic alkynes (**1z** and **1aa)** were also examined and it was found that here too the respective amides **2w–2y** and **2z** and **2aa** were isolated in 44–72% yields. Finally, aiming at assessing the scalability of the protocol, the reaction of **1b** was performed on a 1.0-g scale to obtain the amide **2b** without attenuation of yield.

To gain insights into the mechanism; a few potential intermediates were prepared and subjected to the reaction under standard conditions. Firstly acetophenone **3** was treated with aqueous ammonia under the optimized conditions to detect only a trace of **2a** (< 2%) in the reaction (Scheme 2). Subsequently phenacyl iodide **4** was reacted with aqueous ammonia under the standard conditions and here too only a trace of **2a** (<3%) was detected. Alternatively, we screened phenylglyoxal **5** and phenylglyoxalic acid **6** for their reactions with aqueous ammonia under the standard conditions, but these substrates failed to yield any product. The reaction of diiodoalkene **7** or α,α-diiodo ketone **8** also failed to produce **2a**. Notably, **8** under the standard conditions afforded the diketo amide **9** in 67% yield.[18] Reactions of aqueous ammonia with diphenylethylene **10** or hex-1-yn-1-ylbenzene **11** under the standard conditions were unsuccessful but reaction with **1a** in the presence of TEMPO afforded **2a** in 80% yield thereby ruling out the radical mechanism. To assess the role of light the



Scheme 2. Control experiments. *Standard conditions:* aqueous NH_3 (25%, 5.0 equiv.), I_2 (30 mol%), H_2O_2 (2.0 equiv.) in DMSO at room temperature for 3 h in the presence of visible light. Isolated yields after column chromatography are given.



Scheme 3. Plausible mechanism for the transformation terminal alkyne to primary amide.

reaction of **1a** was repeated in the dark at room temperature and it was found that after 3 h of reaction time only 12% of **2a** was formed. Based on these experiments it was apparent that the reaction does not involve either the hydration of the alkyne as observed in most of the other C≡C bond cleavage reactions.

In the light of these results and to rationalize the liberation of CH_2I_2, a plausible mechanism is presented in Scheme 3. It is proposed that first the alkyne is activated by iodine resulting in the iodonium cation **A**. Subsequent hydroamination leads to intermediate **B** *via* loss of NH_4I. Thereafter an aza-enol attack initiated by intermediate **B** onto iodine affords α,α-diiodo intermediate **C** *via* loss of a second molecule of NH_4I. The intermediate **C** undergoes hydrolysis offering **D** which upon C–C bond cleavage furnished the amide **2** with elimination of CH_2I_2. This CH_2I_2 under the influence of visible light releases iodine *via* formation of the Criegee intermediate (CH_2OO) which acts as the catalyst in the reaction.[19] The formation of CH_2I_2 during the reaction was also mapped *via* a ^{1}H NMR experiment (Figure 2). In this experiment the

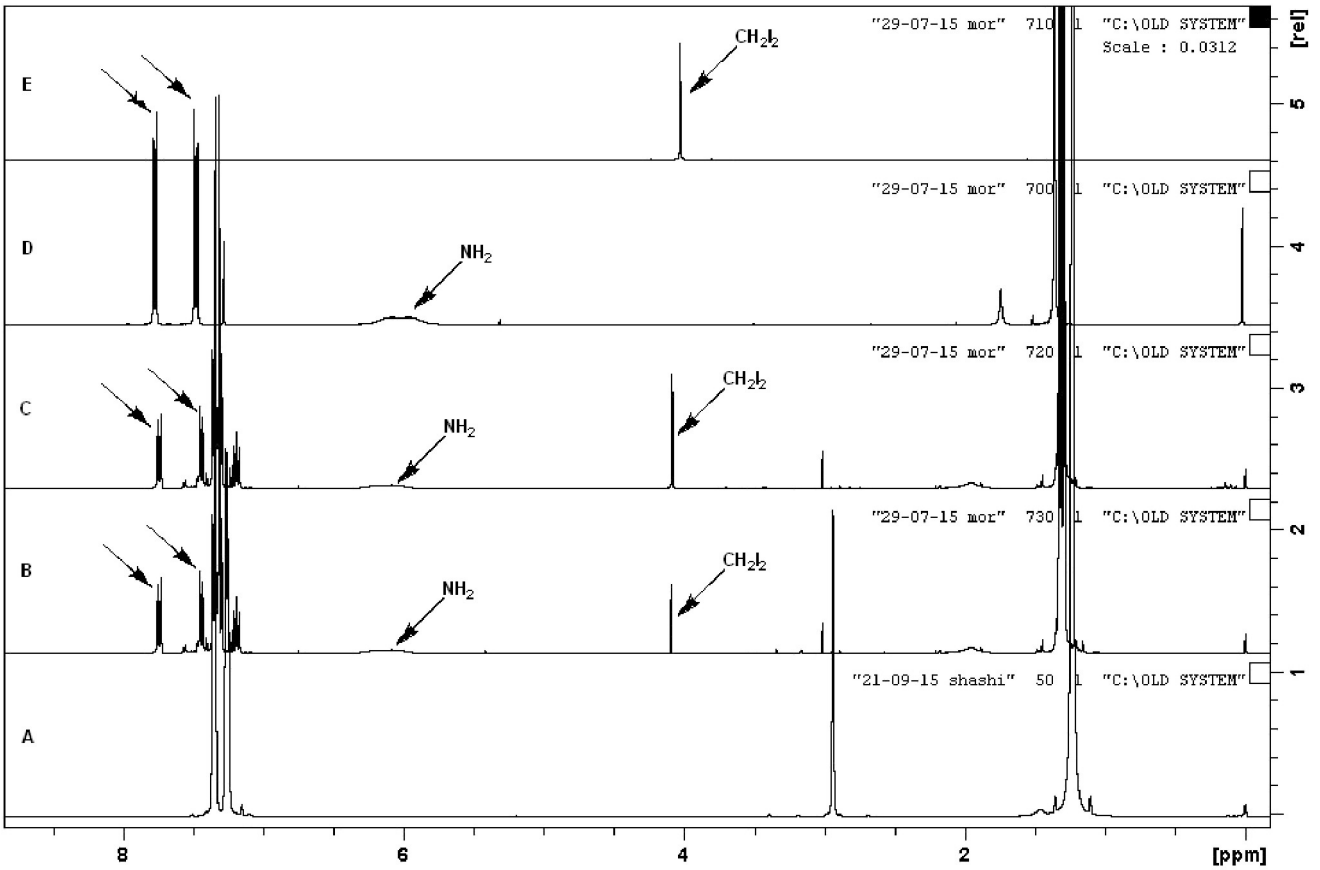


Figure 2. Mapping of CH_2I_2 *via* ^{1}H NMR experiments. (**A**) ^{1}H NMR spectrum of **1b**. (**B**) ^{1}H NMR spectrum of crude reaction mixture of **2b**. (**C**) ^{1}H NMR spectrum of a mixture of crude reaction mixture doped with CH_2I_2. (**D**) ^{1}H NMR spectrum of pure **2b**. (**E**) ^{1}H NMR spectrum of CH_2I_2.

^{1}H NMR spectrum of the reaction mixture (**B**) was compared with that of the starting alkyne (**A**), product (**D**) and commercial CH_2I_2 (**E**). As we noticed minor deviations in the chemical shift of the signal for CH_2I_2 as compared to its authentic sample we recorded another spectrum of a reaction mixture doped with CH_2I_2 (**C**). Herein we observed only one signal for the CH_2I_2 which implied that the minor shift may have been due to the mixture of reagents. Simultaneously H_2O_2 reacts with NH_4I to liberate NH_4OH and HOI that acts as source of $I^{\oplus}$.[20]

In conclusion, we have disclosed an iodine-catalyzed direct transformation of terminal alkynes to primary amides *via* a C≡C bond cleavage reaction under oxidative conditions at room temperature. This updates the literature concerning the transformation of primary alkynes to other useful products. The reaction proceeds *via* initial hydroamination of the acetylenic bond followed by liberation of one carbon as CH_2I_2 which becomes the source of iodine under the visible light. This C≡C bond cleavage strategy is attractive not only because of the use of an inexpensive catalyst and metal-free mild reaction conditions but also because it employs readily available starting materials which can be used without preliminary functionalization.

Experimental Section

General Procedure for the Transformation of 1 to 2 as Exemplified for 2b

To a stirred solution of 1-(*tert*-butyl)-4-ethynylbenzene **1b** (0.2 g, 1.26 mmol) in DMSO (5 mL) was added molecular iodine (0.097 g, 0.38 mmol), aqueous NH_3 (25%) (107 μL, 6.3 mmol) and H_2O_2 (35%) (86 μL, 2.52 mmol) were then added to the reaction mixture at room temperature and the reaction was allowed to continue for 3 h under visible light (150 W tungsten filament lamp) Thereafter the reaction was quenched by the addition of $Na_2S_2O_3$ (10% w/w aqueous, 10 mL) and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic fractions were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude product thus obtained was purified by chromatography over a column of silica gel using hexanes/EtOAc (6.0:4.0, v/v) as eluent to afford the desired product 4-*tert*-butylbenzamide[21] (**2b**) as a white solid; yield: 0.205 g (92%); mp 170–172 °C [lit. 168–170 °C]; R_f = 0.42 (hexane: EtOAc, 6:4, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 6.14 (bs, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 35.1, 125.7, 127.4, 130.6, 155.6, 169.7; MS (ESI$^+$): m/z = 178.2.

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