Organic & Biomolecular Chemistry

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Direct transformation of arylpropynes to acrylamides *via* a three-step tandem reaction†

Cite this: DOI: 10.1039/c3ob42444h

Received 6th December 2013,
Accepted 28th January 2014

DOI: 10.1039/c3ob42444h

www.rsc.org/obc

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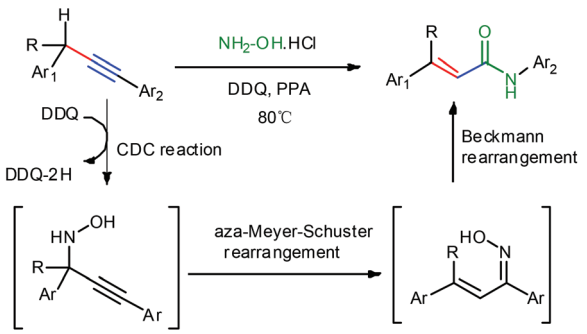
A novel and metal-free acrylamides formation between arylpropynes and hydroxylamine hydrochloride through sp^3 C–H and C–C bond cleavage has been achieved with DDQ as an oxidant. The mechanistic study shows that the acrylamides are formed through a three-step tandem sequence, including cross-dehydrogenative-coupling (CDC) reaction, aza-Meyer–Schuster rearrangement and Beckmann rearrangement.

Various acrylamide derivatives have been studied to have many different biological activities such as anticancer, antimitotic, anti-oxidant, and seed-germination inhibitory effects.[1] Additionally, acrylamides and their derivatives are employed in a wide range of organic reactions, which include nucleophilic additions, cycloaddition reactions, and cyclization reactions, to name just a few.[2] They are also extensively used in the synthesis of polymeric materials.[3] Accordingly, establishing methods to form acrylamide derivatives is of long-standing interest. The most prevalent strategy for acrylamide derivative formation relies heavily on the interconverison of activated acrylacid derivatives with an amine in the presence of a coupling reagent.[4]

Recently, the direct transition-metal-catalyzed transformation of hydrocarbon molecules into corresponding acrylamides has attracted considerable attention and has been the focus of a significant number of studies, owing to not only its fundamental scientific appeal but also its potential utility in organic synthesis.[5] Substituted acrylamides were directly synthesized *via* palladium-catalyzed aminocarbonylation of a variety of alkylamines with alkyl alkynes and a strong acidic medium[6] or in the presence of organic iodides,[7] *p*-TsOH, H_2 [8] or ionic liquid [bmim][Tf_2N].[9] An alternative method for an iron-catalyzed direct transformation of 1,3-diarylpropenes reacted with azides into corresponding acrylamides *via* an oxidative rearrangement was reported by Jiao *et al.*[10]

However, it is worth noting that a direct metal-free method for the preparation of acrylamides through direct C–H or C–C bond activation (cleavage) is still an extremely attractive yet challenging task, and very few metal-free approaches to acrylamides have been reported. In a recent project, our group has demonstrated an atom-efficient and transition metal-free reaction between diarylpropenes and hydroxylamine hydrochloride using DDQ as a promoter to generate corresponding acrylamides.[11] In light of our recent success in this oxidative amidation reaction of diarylpropenes, we turned our attention to the much more challenging amidation reaction of arylpropynes. Herein, we demonstrate an efficient and direct metal-free transformation of arylpropynes into corresponding acrylamides *via* a three-step tandem reaction of a CDC reaction, aza-Meyer–Schuster rearrangement and Beckmann rearrangement in the presence of hydroxylamine hydrochloride and DDQ (Scheme 1).

An initial study was carried out using 1-phenyl-3-(4-chlorophenyl)-propyne **1a** and hydroxylamine hydrochloride as the substrates, DDQ was used as the oxidant to examine suitable reaction conditions, and the results are summarized in Table 1. Several solvents including DCE, 1,4-dioxane, DMF, CH_3NO_2, CH_3CN, CH_3CN–HOAc, CH_3CN–HCOOH were



Scheme 1 DDQ-promoted transformation of arylpropynes into acrylamides.

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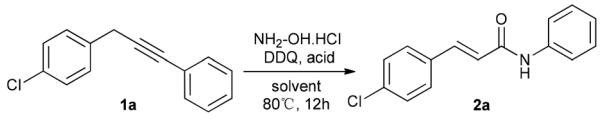
†Electronic supplementary information (ESI) available: Experiment procedure and NMR data. See DOI: 10.1039/c3ob42444h

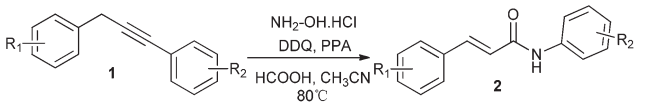
Table 1 Screening of reaction conditions[a]

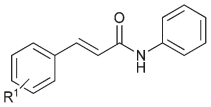
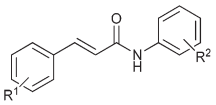
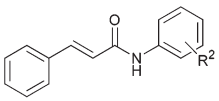


Entry	Acid	Solvent	Oxidant	Yield[b] (%)
1	PPA	DCE	DDQ	52
2	PPA	1,4-Dioxane	DDQ	40
3	PPA	CH_3NO_2	DDQ	63
4	PPA	DMF	DDQ	13
5	PPA	MeCN	DDQ	72
6	PPA	MeCN–HOAc	DDQ	75
7	PPA	MeCN–HCOOH	DDQ	81
8	*p*-TSA	MeCN–HCOOH	DDQ	76
9	H_2SO_4	MeCN–HCOOH	DDQ	21
10	MsOH	MeCN–HCOOH	DDQ	77
11	—[c]	MeCN–HCOOH	DDQ	45
12	PPA	MeCN–HCOOH	BQ	27
13	PPA	MeCN–HCOOH	TBHP	n.d.
14	PPA	MeCN–HCOOH	$PhI(OAc)_2$	n.d.

[a] Reaction conditions: **1a** (1 mmol), $NH_2OH{\cdot}HCl$ (0.5 mmol), DDQ (0.75 mmol), acid (0.15 mmol), solvent (1.5 mL), co-solvent (1.5 mL), stirred at 80 °C over 12 h. [b] Isolated yield. [c] No addition of acid. PPA = polyphosphoric acid. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. TBHP = *tert*-butyl hydroperoxide (70% aqueous solution).

Table 2 Direct transformation of 1,3-diarylpropynes **1** into the acrylamides **2**[a]



Entry	R^1, R^2	Product		Yield[b] (%)
1	4-Cl, H **1a**		**2a**	81
2	4-F, H **1b**		**2b**	83
3	4-Br, H **1c**		**2c**	77
4	2-Cl, H **1d**		**2d**	72
5	3-F, H **1e**		**2e**	78
6	2,4-Cl, H **1f**		**2f**	85
7	2,6-Cl, H **1g**		**2g**	82
8	4-CH_3, H **1h**		**2h**	52
9	4-CH_3O, H **1i**		**2i**	16
10	4-F, 4-Cl **1j**		**2j**	88
11	4-Cl, 2,6-Cl **1k**		**2k**	86
12	4-Br, 4-Br **1l**		**2l**	83
13	4-CH_3, 4-CH_3 **1m**		**2m**	31
14	4-Cl, 4-CH_3 **1n**		**2n**	72
15	4-CH_3, 4-Cl **1o**		**2o**	61
16	H, 4-Br **1p**		**2p**	75
17	H, 4-Cl **1q**		**2q**	77
18	H, 4-CH_3 **1r**		**2r**	67
19	H, H **1s**		**2s**	72

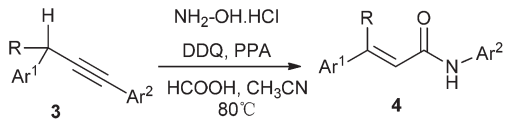
[a] Reaction conditions: **1** (1 mmol), $NH_2OH{\cdot}HCl$ (0.5 mmol), DDQ (0.75 mmol), PPA (0.15 mmol), HCOOH (1.5 mL), MeCN (1.5 mL) stirred at 80 °C for 12 h. [b] Yield of the isolated product.

screened in the presence of PPA at 80 °C (Table 1, entries 1–7). Moderate yields of the desired product **2a** were obtained using CH_3NO_2, DCE and 1,4-dioxane as a solvent (Table 1, entries 1–3). Considerable amounts of undesired products were formed and resulted in lower yield using DMF (Table 1, entry 4). It should be noted that a good yield of the desired product **2a** was obtained using CH_3CN and CH_3CN–HOAc (Table 1, entries 5 and 6). Fortunately, when CH_3CN–HCOOH instead of CH_3CN and CH_3CN–HOAc were used as the solvent, **2a** was obtained in the highest yield of 81% (Table 1, entry 7). To establish the reaction conditions that improve the reactivity, several acids such as *p*-TSA, H_2SO_4, MsOH, and PPA were tested in CH_3CN–HCOOH (1 : 1) at 80 °C (Table 1, entries 7–10); the target acrylamide product **2a** could be obtained in 21%–81% yields. Only 45% desired product was isolated in the absence of other acids (Table 1, entry 11). It was found that PPA as the acid showed relatively higher efficiency compared with other acids and thus was chosen as the acid for further optimization. Furthermore, BQ, TBHP and $PhI(OAc)_2$ were screened as the oxidant. However, large amounts of undesired by-products were observed and the yields were remarkably diminished when BQ was used as the oxidant (Table 1, entry 12). Both TBHP and $PhI(OAc)_2$ used as the oxidant instead of DDQ demonstrated very poor activity and no desired product was detected (Table 1, entries 13 and 14).

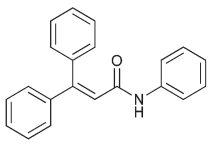
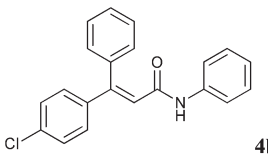
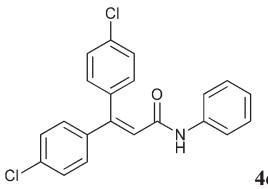
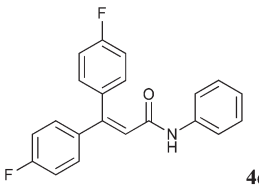
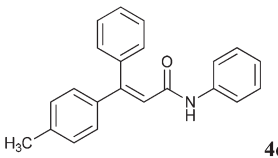
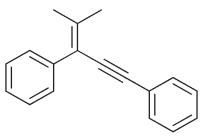
With the optimized reaction conditions established, various substrates were subjected to the reaction and representative results are summarized in Table 2. To our delight, a variety of substituted 1,3-diarylpropynes could easily be converted into the corresponding acrylamides in moderate to good yields (up to 88%). It is noteworthy that various electron-withdrawing substituents on the aromatic rings were compatible with the process and did not affect the efficiency of the reaction (Table 2, entries 1–7, 10–12 and 16–18). Fluoride, chloride, and bromide substituents reacted well, thus leading to the corresponding acrylamides in high yields (72–88%); especially excellent yields were obtained when the two phenyl rings of the substrate had electron-withdrawing groups respectively (Table 2, entries 10–12). In comparison, when 1,3-diarylpropynes bearing electron-donating substituents like the methyl group on the aromatic ring were used, considerable amounts of unwanted by-products were formed and the reaction resulted in lower yields (31–67%) (Table 2, entries 8, 13 and 18). Furthermore, when the substrates bearing *para*-methoxyl groups on the aromatic ring were employed, only 16% acrylamide product were detected (Table 2, entry 9). Surprisingly, no regioisomeric acrylamides were detected when a variety of mono- or asymmetrically disubstituted 1,3-diarylpropynes were employed, the clearest example was the formation of **2n** and **2o**; it was found that there was no trace of **2o** in the isolated **2n** according to the experimental data, and *vice versa* (see NMR charts in ESI†). Regioisomers were generally obtained when unsymmetric 1,3-diarylpropenes reacted with various nucleophilic reagents.[11,12] Additionally, it was found that the "R^1" substituent on the benzene ring exerts more influence on the reaction in comparison with the "R^2" substituent (Table 2, entries 1, 3, 8 and 16–18).

Encouraged by the above results, we further investigated the reactions between 1,3,3-triarylpropynes and hydroxylamine hydrochloride under the standard reaction conditions. To our delight, several triarylpropynes could successfully afford the corresponding acrylamides in moderate to good yields. As indicated in Table 3, good yields in the acrylamides products **4b**, **4c**, **4d** were obtained when 1,3,3-triarylpropynes bearing electron-withdrawing substituents were employed as the substrates (Table 3, entries 2–4), while considerable amounts of undesired by-products were formed and no target product was obtained with the methyl group on the aromatic ring (Table 3, entry 5). Unfortunately, when 3-isopropyl-1,3-diphenylpropyne was used as the substrate, no acrylamide products were generated and the enyne **4f** was detected (Table 3, entry 6). We speculated that the enyne may be generated by dehydrogenation with DDQ.[13]

Table 3 Direct transformation of 1,3,3-triarylpropynes **3** into the acrylamides **4**[a]



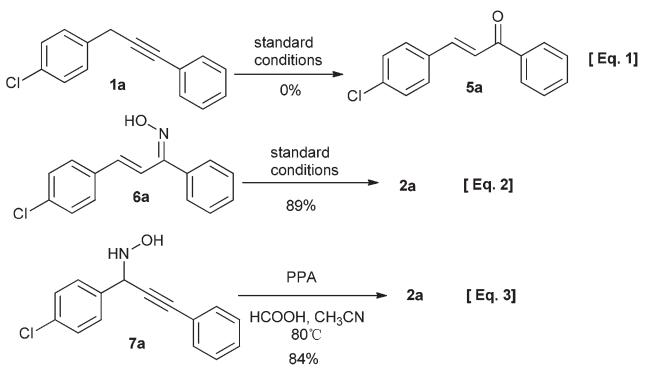
3 **4**

Entry	Product	Yield[b] (%)
1	 **4a**	65
2	 **4b**	71
3	 **4c**	75
4	 **4d**	80
5	 **4e**	Trace
6	 **4f**	31

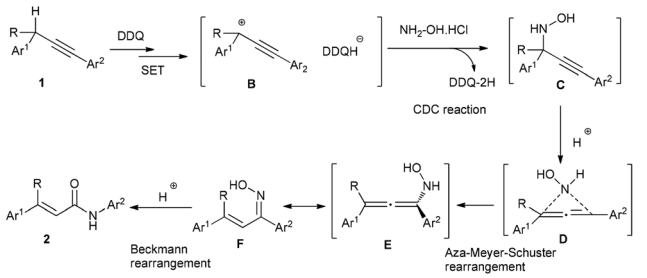
[a] Reaction conditions: **1** (1 mmol), $NH_2OH{\cdot}HCl$ (0.5 mmol), DDQ (0.75 mmol), PPA (0.15 mmol), HCOOH (1.5 mL), MeCN (1.5 mL) stirred at 80 °C for 12 h. [b] Yield of the isolated product.

Additional mechanistic studies with possible key intermediates have been investigated (Scheme 2). One possible pathway for this transformation is likely to be an oxidation of diarylpropyne to chalcone with a subsequent Beckmann rearrangement. However, when **1a** was tested in the absence of hydroxylamine hydrochloride under the standard reaction conditions, no chalcone **5a** was observed (eqn (1)). In addition, when the reaction of ketoxime **6a** was carried out under the standard reaction conditions, the target acrylamide **2a** was produced in 89% yield (eqn (2)). These results suggest that the reaction does not undergo oxidation of diarylpropyne to chalcone with a subsequent Beckmann rearrangement. To further probe the mechanism of this novel transformation, propargylic hydroxylamine **7a** was synthesized from propargylic alcohols and could also successfully afford the target acrylamide **2a** in 84% yield under the standard reaction conditions (eqn (3)).[14] All these results indicate that the ketoxime **6a** and propargylic hydroxylamine **7a** may be involved as the key intermediates in this transformation.

Although the mechanism is not completely clear yet, a plausible mechanism for our methodology is hypothesized on the basis of the literature[9–13,15] and the above mechanistic studies (Scheme 3). Initially, the reaction is a single-electron



Scheme 2 Investigation of the possible key intermediates.



Scheme 3 Plausible mechanism for the formation of **2**.

transfer (SET) process between substrates **1** and DDQ to form the propargyl cation **B**. The cation **B** with a hydroxylamine hydrochloride gave rise to the C–N bond coupling product **C** by a subsequent CDC reaction process. Subsequently, **C** undergoes a [1,3] shift of the –NH-OH group to the transition state **D**, which further generates allene **E** through the aza-Meyer–Schuster rearrangement in the presence of an acid. Then rapid tautomerization of allene **E** would lead to the ketoxime **F**. Subsequently the target acrylamide **2** could be generated from the ketoxime **F** through the Beckmann rearrangement in the presence of an acid.

In summary, we have demonstrated a novel and metal-free method for the direct transformation of arylpropynes into corresponding acrylamides by one C(sp^3)–H, and one N–H, one C–C bond cleavages. The mechanistic study shows that the acrylamides are formed through a three-step cascade sequence involving a hetero-CDC reaction with a subsequent tandem aza-Meyer–Schuster rearrangement and Beckmann rearrangement. To the best of our knowledge, this is the first direct transformation of arylpropynes to acrylamides without a metal catalyst. This method provides a new and unique strategy to functionalize simple and readily available hydrocarbon molecules by a CDC reaction with subsequent tandem rearrangements. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our group.

We are grateful to the Natural Science Foundation of China (no. 20972113/B020502) for support.

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