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Water-controlled selective preparation of α-mono or α,α′-dihalo ketones *via* catalytic cascade reaction of unactivated alkynes with 1,3-dihalo-5,5-dimethylhydantoin†

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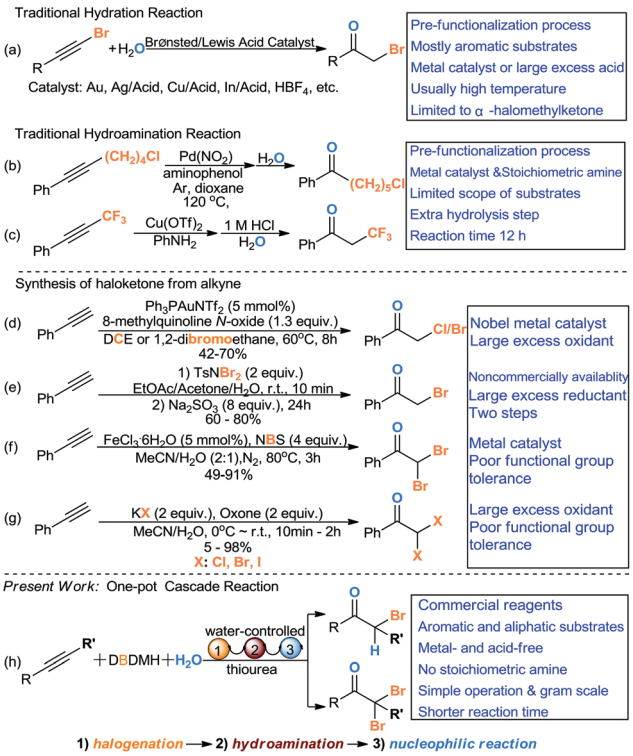
The control of a reaction that can produce multiple products from the same starting material is a highly attractive and challenging concept in organic synthesis. An efficient protocol for the selective synthesis of α-mono or α,α′-dihalo ketones *via* a water-controlled three-component thiourea-catalyzed cascade reaction of unactivated alkynes, 1,3-dihalo-5,5-dimethylhydantoin and water has been developed. α-Monohaloketones were obtained in aqueous acetone at 45 °C; conversely, α,α′-dihalo ketones were formed with pure water as the sole solvent at room temperature.

Introduction

The control of a chemical reaction to efficiently and selectively produce a series of distinct valuable molecules from the same starting material is a highly attractive concept, but represents a significant challenge in synthetic chemistry.[1] On the other hand, one-pot multi-bond forming processes, including multi-component cascade reactions, are the best choice for attaining atom and step economy and thus for developing ideal synthetic procedures for complex molecules.[2] Selective halogenation processes could be of great benefit as organohalogen compounds are widely utilized.[3] For example, α-mono and α,α′-dihalo ketones are important structural motifs and intermediates for fine chemicals, pharmaceuticals, agrochemicals and natural products.[4] Tremendous efforts have been devoted to the construction of such structures during the past few decades.[5] However, the direct production of α-haloketones from simple alkynes represents a highly attractive alternative, given the abundance and accessibility of these starting materials. For this reason, the addition of water and nitrogen across carbon–carbon triple bonds (hydration[6] and hydroamination[7]) has long been pursued as a means to access α-haloketones and related analogues (Scheme 1a–c). One method to prepare α-monohaloketone is by gold-catalyzed oxidation of terminal alkynes as reported by Zhang (Scheme 1d).[8]



Scheme 1 Synthesis of α-haloketones.

However, the $Ph_3PAuNTf_2$ catalyst and 8-methylquinoline *N*-oxide are expensive and the low atom efficiency of this process has limited its application. Phukan *et al.* treated unactivated alkynes with $TsNBr_2$ to form α-monohaloketones

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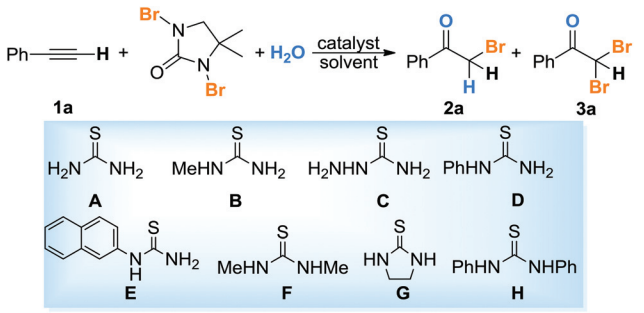
(Scheme 1e).[9] The use of noncommercially available $TsNBr_2$ has limited the application of this method. Li *et al.* reported the $FeCl_3$-catalyzed bromination of alkynes by using *N*-halosuccinimide (Scheme 1f),[10] but only α-monobromoketones were formed. Madabhushi *et al.* employed oxyhalogenation of alkynes by using oxone and halide salt to achieve the same goal (Scheme 1g).[11] However, these two methods bear several limitations, such as undesirable side reactions, requiring the use of a metal catalyst or an excessive amount of oxidant, and they suffer from a limited substrate scope. Although much progress has been made, the divergent synthesis of haloketones, especially α-monohaloketones, from unactivated alkynes and green halogenating reagents under metal-free, additive-free and oxidant-free conditions remains elusive.

We recently detailed the regio- and stereoselective synthesis of *Z*-tosylacrylate through the addition of a proton to the C≡C triple bond followed by C_{sp^2}–S bond formation using an electrophilic sulfur source.[12] We speculated on the possibility that conditions could be developed to convert alkynes to α-mono and α,α′-dihalo ketones in one synthetic operation. Such cascade processes are highly desirable in organic synthesis, because potentially difficult work-up and isolation steps can be avoided and the generation of chemical waste is minimized.[13] In particular, we envisioned a scenario in which the starting unactivated alkyne is initially halogenated to an halonium ion intermediate,[14] which would then undergo hydroamination to afford the β-haloenamine species.[15] Subsequent interception of this intermediate by a different nucleophile would potentially enable the selective formation of α-mono and α,α′-dihalo ketones (Scheme 1h). 1,3-Dihalo-5,5-dimethylhydantoins are perfect halogenating reagents in synthetic chemistry because they are cheap and readily available on a large scale, stable in air and safe for humans; and notably, the reaction generates easily degradable by products.[16] In continuation of our ongoing research on alkyne chemistry,[17] we herein report for the first time simple and mild conditions for the highly chemo- and regioselective synthesis of α-mono and α,α′-dihaloketone products through the water-controlled three-component thiourea-catalyzed cascade reaction of unactivated alkynes, 1,3-dihalo-5,5-dimethylhydantoin and water under metal-free, additive-free and oxidant-free conditions.

Results and discussion

To test our hypothesis, phenylacetylene **1a** was treated with 1,3-dibromo-5,5-dimethyldantoin (DBDMH, 1.2 equiv.), water (2.5 equiv.) and thiourea (cat. A, 15 mmol%) as a catalyst in acetone (0.5 ml) at room temperature. Pleasingly, α-bromoacetophenone **2a** was afforded in 47% NMR yield based on 61% conversion of the starting material **1a** after 8 h (Table 1, entry 1). To increase the reaction efficiency, a series of substituted thioureas were investigated (entries 2–8). The results revealed that ethylene thiourea (catalyst G, entry 7) was a superior catalyst with an 88% yield. In the absence of thiourea, only a trace amount of **2a** was detected, even after running the reaction for 72 h (entry 9). When other bromine sources such as *N*-bromosuccinimide (NBS), phenyltrimethylammonium tribromide (TBAB), and bromotrichloromethane (CCl_3Br) were applied instead of DBDMH, the conversions and selectivities were unsatisfactory (entries 10–12). To advance the process further, other ketone solvents including pure ketone and cyclohexanone were tested, and it was found that they could also promote the reaction efficiently to give 87% and 71% yields, respectively (entries 13 and 14). Thus, we chose aqueous acetone as the reaction medium due to practical (easy to handle and cheap) and safety reasons. Subsequent examination of the effect of the reaction temperature proved that 45 °C was appropriate for the reaction (entries 15 *vs.* 7 and 16). Given that the water played a critical role in hydroamination and hydration reaction, the dosage of water was evaluated (entries 17–21). A quantitative yield (96%) was obtained in 6 hours when the amount of water reached 10 μl (6 equiv.

Table 1 Optimization of reaction conditions[a]



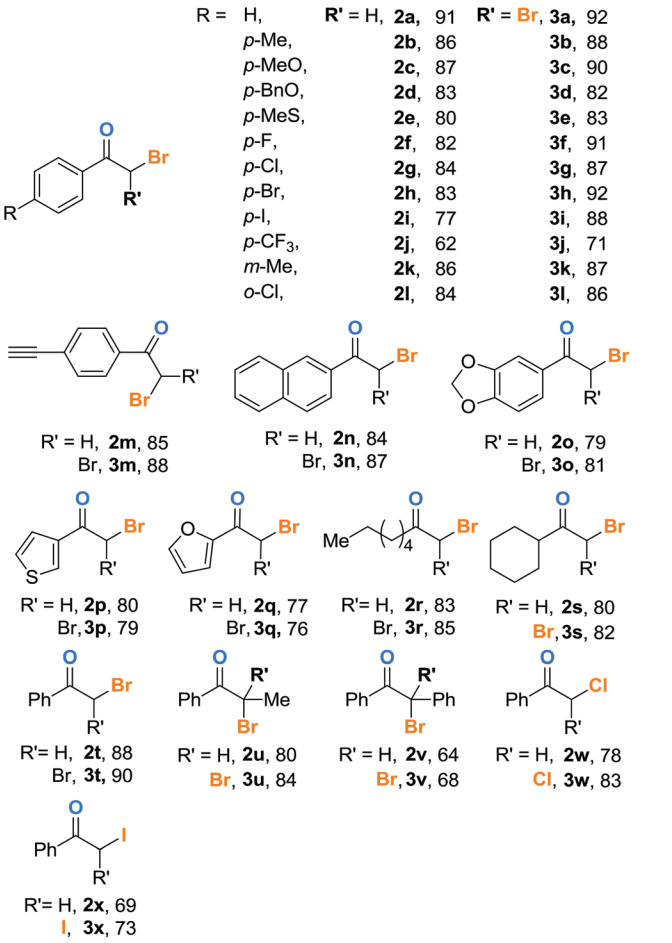
Entry	Catalyst	Solvent ($V_{acetone}$: V_{H_2O})	Temp.	Yield[b] 2a	Yield[b] 3a
1	Cat. A	Acetone : H_2O (100 : 1)	RT	47	n.d
2	Cat. B	Acetone : H_2O (100 : 1)	RT	54	n.d
3	Cat. C	Acetone : H_2O (100 : 1)	RT	67	n.d
4	Cat. D	Acetone : H_2O (100 : 1)	RT	75	n.d
5	Cat. E	Acetone : H_2O (100 : 1)	RT	54	n.d
6	Cat. F	Acetone : H_2O (100 : 1)	RT	69	n.d
7	Cat. G	Acetone : H_2O (100 : 1)	RT	88	n.d
8	Cat. H	Acetone : H_2O (100 : 1)	RT	70	n.d
9	—	Acetone : H_2O (100 : 1)	RT	18	Trace
10[c]	Cat. G	Acetone : H_2O (100 : 1)	RT	59	12
11[d]	Cat. G	Acetone : H_2O (100 : 1)	RT	30	16
12[e]	Cat. G	Acetone : H_2O (100 : 1)	RT	21	Trace
13	Cat. G	Acetone	RT	87	n.d
14	Cat. G	Cyclohexanone	RT	71	n.d
15	Cat. G	Acetone : H_2O (100 : 1)	45 °C	96	n.d
16	Cat. G	Acetone : H_2O (100 : 1)	70 °C	96	n.d
17	Cat. G	Acetone : H_2O (75 : 1)	45 °C	96	n.d
18	**Cat. G**	**Acetone : H_2O (50 : 1)**	**45 °C**	**96**	**n.d**
19	Cat. G	Acetone : H_2O (10 : 1)	45 °C	45	40
20	Cat. G	Acetone : H_2O (3 : 1)	45 °C	Trace	90
21	Cat. G	H_2O	45 °C	Trace	90
22	**Cat. G**	**H_2O**	**RT**	**n.d**	**94**

[a] Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.1 mmol), DBDMH (0.12 mmol), solvent. [b] Estimated by ^1H NMR using diethyl phthalate as an internal reference. [c] NBS instead of DBDMH. [d] TBAB instead of DBDMH. [e] CCl_3Br instead of DBDMH. rt = room temperature. n.d = no desired product.

entry 18). To our delight but unexpectedly, when the quantity of water was increased to 0.1 ml, α,α′-dibromoacetophenone **3a** rather than **2a** was obtained (entry 19). The unexpected outcomes prompted us to investigate the interesting process in detail. We found that the cascade reaction of alkynes tended to generate **3a** in water rich solvent. With a mixed solvent of acetone/water (3 : 1), a complete conversion into **3a** was observed (entry 20). The use of water as the sole solvent for organic synthesis has become popular and received substantial interest because water is a green and abundant natural resource which can be easily obtained.[18] Much to our delight, the reaction of **1a** afforded the desired **3a** in 90% yield when water was employed as the sole reaction medium (entry 21). We were quite satisfied to see that our reaction proceeded at room temperature and the yield reached 94% after a reaction time of 4 h (entry 22). Thus, the different reaction conditions for the selective synthesis of **2a** and **3a** have been smoothly optimized, respectively (entries 18 and 22). Mild reaction conditions, shorter reaction times, cost-effectiveness, operational simplicity, excellent yields and high chemoselectivity make this transformation an alternative method for the straightforward preparation of a set of distinct α-haloketones.

With the optimized reaction conditions in hand, the substrate scope of the unactivated terminal alkynes was first examined, and the results are summarized in Table 2. The electronic and steric effects of different functional groups on the benzene ring of phenylacetylene **1** were examined (**1a–1l**). It was found that, regardless of the electron-neutral, -donating, or -withdrawing groups installed on the substrates, all afford the desired products in good to high yields. In addition, a wide range of functional groups were tolerated including methyl, alkoxy (**MeO** and **BnO**), oxidizable thioether (**MeS**), halides (**F**, **Cl**, **Br**, **I**) and trifluoromethyl groups at the different positions of phenylacetylenes. Given that *p*-diethynylbenzene (**1m**) contains two potential alkynyl groups, we were pleased to find that only mono-bromination products **2m** and **3m** were obtained without any double addition products. Fused aromatic substituted ethynes (**1n–1o**) could also be transformed into the corresponding products in good yield. Electron-rich heterocycle-containing alkynes (**1p–1q**) are also suitable substrates for this transformation. However, electron-poor alkynes, such as 2- and 3-pyridylacetylenes, did not undergo the reaction, likely caused by the low reactivity of the C≡C triple bonds. When aliphatic terminal alkynes (**1r–1s**) were employed for the transformation, the corresponding products were obtained in good yields. The internal alkyne, which is usually much less reactive than the terminal alkyne, was also tested. Subjecting the substrate ethyl trimethyl(phenylethynyl) silane **1t** to the standard reaction conditions could smoothly afford **2t** and **3t**, allowing access to phenylacetylene *via* deprotection of the TMS group. Compared to alkyl-substituted phenylacetylene (**1u**), the aryl-substituted one (**1v**) exhibited relatively poor reactivity and the examples indicate that steric hindrance plays a key role in these transformations. Moreover, this protocol could also be effectively applied for the divergent synthesis of α-chloroketone and α-iodoketone in good yields

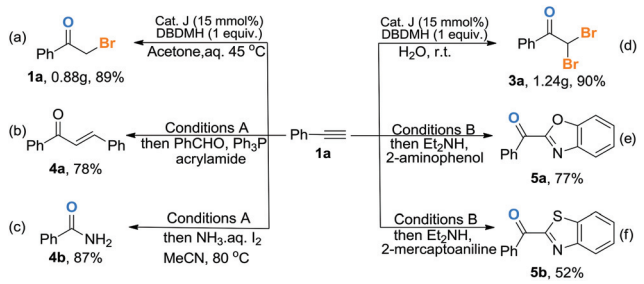
Table 2 Reaction scope[a]



[a] Condition A: synthesis of α-mono haloketones, alkyne **1** (0.25 mmol), DBDMH (0.3 mmol), aqueous acetone (1 ml, $V_{acetone} : V_{water} = 50 : 1$), 45 °C; Condition B: synthesis of α-dihalo ketones, alkyne **1** (0.25 mmol), DBDMH (0.3 mmol), water (1 ml), room temperature; isolated yields are reported.

(**2w–2x**, **3w–3x**). When methyl propiolate was employed as a substrate, the formation of undesired side-reaction products was inevitable because of higher reactivity of propargylic carboxylates in comparison to that of unactivated alkynes.

For the small-scale reaction, 1.2 equiv. of DBDMH was required, and decreasing the amount of bromide reagents would decrease the yield. Delightedly, the use of 1.0 equiv. of DBDMH could afford the desired product (**2a** 89% and **3a** 90% yields, respectively) with an increase of the scale of the reaction by 20-fold (Scheme 2a and d), demonstrating the synthetic utility of this protocol from a practical point of view. Importantly, the products were easily recrystallized to afford pure α-haloketones. The present cascade reaction provides a simple and straightforward access from readily available materials (alkynes, DXDMH and water) to functionalized α-haloketones, which permits rapid access to various important compounds. For instance, the chalcone **4a** was isolated in 78% yield by the combination of the cascade reaction

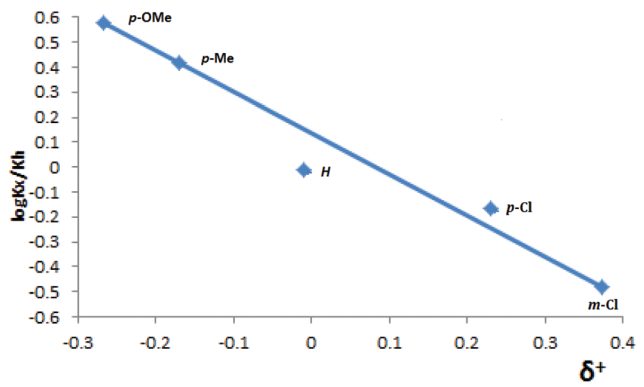


Scheme 2 Applications to transforming reactions.

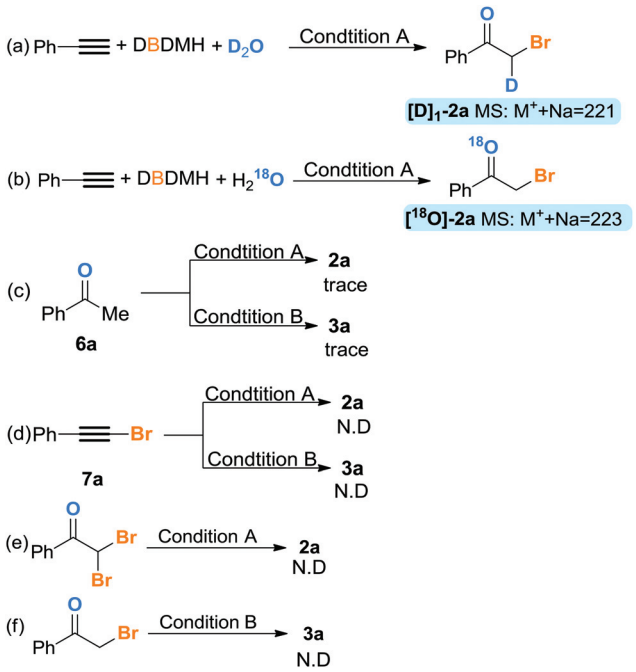
(condition A) and a subsequent three-component reaction (Scheme 2b).[19] Moreover, coupled with a subsequent amination of α-bromomethyl ketone with I_2 and ammonium hydroxide simple workup, this reaction led to benzamide **4b** in 87% overall yield (Scheme 2c).[20] Furthermore, one-pot, sequential cascade reaction of alkynes with DBDMH followed by Et_2NH/DMF mediated cyclization was found to provide **5a** and **5b** in 77% and 52% yields, respectively (Scheme 2e and f).[4g]

To gain more insight into the mechanism of the present catalytic reaction, a Hammett plot was constructed for the migration of *para*- and *meta*-substituted ethynylbenzene. In this way, we hoped to gain an understanding of the type of intermediates that were involved in the reaction. Utilizing different substituted ethynylbenzenes, the required kinetic data were obtained by GC-MS analysis of reaction aliquots. The reactivity order for ethynylbenzene is as follows: *p*-OMe (k_X/k_H = 3.9) > *p*-Me (2.6) > H (1.0) > *p*-Cl (0.65) > *m*-Cl (0.32).[21] As shown in Scheme 3, a linear correlation with a slope (Hammett's ρ^+ value) of −1.63 was observed. This large, negative ρ value suggests that the reaction proceeds *via* the intermediacy of a bromirenium ion species and provides strong evidence against mechanisms in which a negatively charged, or radical (neutral) intermediate would be required before or at the rate-determining step.

Next, several control experiments were performed. First, when 5 equiv. of D_2O was added to acetone, the reaction afforded 92% incorporation of deuterium at the α positions of **[D]$_1$-2a** (detected by MS, Scheme 4a), which indicated that the



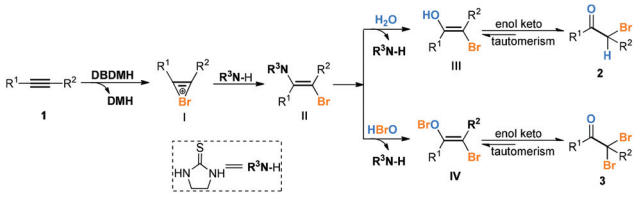
Scheme 3 Hammett plot for the competitive cascade reaction.



Scheme 4 Control experiments.

α-hydrogen atom of α-bromoacetophenone originated from water. The isotope labeling experiment was then performed in the presence of $H_2{}^{18}O$ (5 equiv.) and **^{18}O-2a** was detected (Scheme 4b). On the basis of all these results, we proposed that this transformation was preferred to an enol keto tautomerism pathway. The treatment of acetophenone **6a** under the standard conditions only afforded a trace amount of the desired product **2a** (Scheme 4c). When bromoethynyl benzene **7a** was subjected to the standard conditions, no desired products were detected (Scheme 4d). These results ruled out the possibility of **6a** and **7a** as intermediates of the transformation. It was found that **3a** failed to result in **2a** under the standard conditions A (Scheme 4e). Meanwhile, **2a** also could not lead to **3a** under the standard conditions B (Scheme 4f).

On the basis of the above observations and previous reports,[14] the plausible catalytic path is proposed in Scheme 5. Initially, the alkyne moiety of the substrate is brominated by DBDMH to form bromirenium ion I with concomitant release of 5,5-dimethylhydantoin (DMH). Subsequently, the regio- and anti-selective nucleophilic addition of the amino group of thiourea to intermediate I generated the β-haloenamine intermediate II. The hydroxyl ion of water displaces the amino



Scheme 5 Proposed mechanism.

group on the intermediate II to regenerate the thiourea catalyst and give the enol intermediate III, which would isomerize to a more stable α-bromoketone **2** through keto–enol tautomerism. When water is used as the sole solvent, an active hypobromous acid (HOBr) intermediate could be generated rapidly.[22] Subsequently, the oxygen atom of HOBr quickly attacks the intermediate II to form the intermediate IV, which triggers another keto–enol tautomerism process to afford target products **3**. In this approach, DBDMH serves as an activating agent and bromine source.

Conclusions

In summary, we have developed a water-controlled three-component thiourea-catalyzed cascade reaction of unactivated alkynes, 1,3-dihalo-5,5-dimethylhydantoin and water for the efficient divergent synthesis of α-mono or α,α′-dihalo ketones under metal-free, additive-free and oxidant-free conditions. Conducting the reaction in aqueous acetone, α-monohalo ketones are produced completely selectively while α,α′-dihalo ketones are exclusively formed with water as the sole solvent. The newly developed protocol has advantages over the previous methods: (1) the well-matched reactivity of alkynes with ethylene thiourea and water results in simple reaction conditions with easy operationality, where metal catalysts, additives and high temperatures are not required; (2) in contrast to the previous methods, both terminal and internal alkynes, as well as heteroaromatic alkynes are suitable for cascade reaction; and (3) this protocol does not require pre-functionalization of the alkynes and thus it provides a better and practical alternative to the existing procedures. Finally, the proposed mechanism was carefully explored through the Hammett plot, deuterium-labeling experiments, control experiments, and we expect that this detailed study would shed light on the scope and potential of the activation strategy of unactivated alkynes.

Experimental

General information

Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers and used without further purification. All reagents were weighed and handled in air at room temperature. Chromatographic purifications were carried out on a Biotage Isolera Four instrument. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz by using a Bruker Avance 400 spectrometer. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS). The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet. IR spectra were recorded on a Nicolet iS10 FT-IR spectrometer and only major peaks were reported in cm^{-1}. Mass spectra were performed on a spectrometer operating on ESI-TOF.

General procedure for the synthesis of α-monohalo ketones 2

To a vial were added alkyne (0.25 mmol), 1,3-dihalo-5,5-dimethylhydantoin (0.3 mmol), ethylene thiourea (0.0375 mmol), and aqueous acetone (1 ml, $V_{acetone} : V_{water} = 50 : 1$), then the contents were stirred at 45 °C. The progress of the reaction was monitored by TLC. Upon completion, the reaction was cooled down to room temperature and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford **2**.

General procedure for the synthesis of α,α′-dihaloketones 3

To a vial were added alkyne (0.25 mmol, 25.5 mg), 1,3-dihalo-5,5-dimethylhydantoin (0.3 mmol), ethylene thiourea (0.0375 mmol), and water (1 mL), then the contents were stirred at room temperature. The progress of the reaction was monitored by TLC. Upon completion, the reaction was mixed with silica gel and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford **3**.

Procedure for the synthesis of chalcone 4a

To a sealed tube were added alkyne (0.25 mmol, 25.5 mg), DBDMH (0.3 mmol, 86 mg), ethylene thiourea (0.0375 mmol), and aqueous acetone (1 ml, $V_{acetone} : V_{water} = 50 : 1$), then the contents were stirred at 45 °C. After completion of the reaction (monitored by TLC), the solution was concentrated under reduced pressure to remove acetone. Then a solution of benzaldehyde (0.2 mmol, 21 mg), triphenylphosphine (0.48 mmol, 125.7 mg) and acrylamide (0.24 mmol, 21 mg) in chloroform (1 mL) was added to the above residue, the reaction mixture was stirred at 90 °C. After completion of the reaction, the reaction mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford **4a**.

Procedure for the synthesis of benzamide 4b

To a sealed tube were added alkyne (0.25 mmol, 25.5 mg), DBDMH (0.3 mmol, 86 mg), ethylene thiourea (0.0375 mmol), and aqueous acetone (1 ml, $V_{acetone} : V_{water} = 50 : 1$), then the contents were stirred at 45 °C. After completion of the reaction (monitored by TLC), the solution was concentrated under reduced pressure to remove acetone. Then a solution of aq. NH_3 (concentration: 28–30%, 0.8 mL) and I_2 (0.7 mmol, 184.5 mg) in MeCN (0.5 ml) was added to the mixture, and the obtained mixture was stirred for 12 hours at room temperature. The mixture was quenched using sat. aq. Na_2SO_3 (10 mL) and extracted with ethyl acetate (20 mL × 3). Then, the organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford benzamide **4b**.

Procedure for the synthesis of α-haloketones 5a and 5b

To a sealed tube were added alkyne (0.25 mmol, 25.5 mg), DBDMH (0.3 mmol, 86 mg), ethylene thiourea (0.0375 mmol), and water (1 mL), then the contents were stirred at 45 °C. After completion of the reaction (monitored by TLC), the solution was concentrated under reduced pressure to remove water. 2-Amino(thio)phenols (0.2 mmol), Et_2NH (0.8 mmol, 60 mg), and DMF (0.5 mL) were stirred at 90 °C under N_2 for another 5 h. After cooling to room temperature, water (20 mL) was added, and the aqueous phase was extracted with ethyl acetate (5 × 20 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford benzo[*d*]oxazol-2-yl(phenyl)methanone **5a** and benzo[*d*]thiazol-2-yl(phenyl)methanone **5b**.

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