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Visible-light-promoted N–H functionalization of O-substituted hydroxamic acid with diazo esters†

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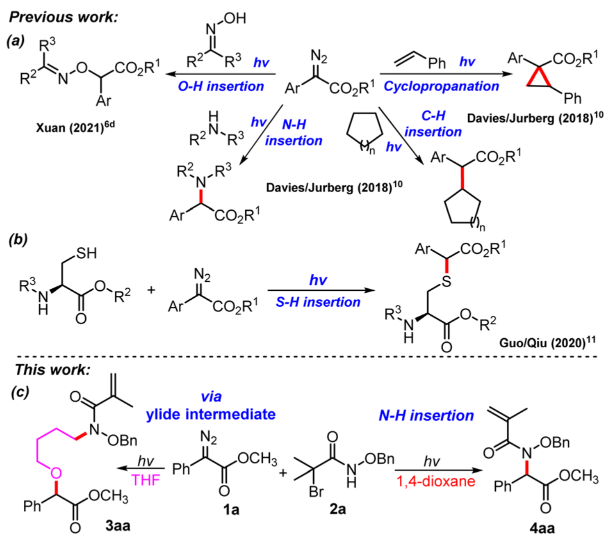
Herein we report an N–H functionalization of O-substituted hydroxamic acid with diazo esters under blue LED irradiation conditions. The present transformations could be performed efficiently under mild conditions without use of catalyst, additive and N_2 atmosphere. Interestingly, when THF and 1,4-dioxane were employed as the reaction solvents, an active oxonium ylide involved three-component reaction and an N–H insertion of carbene species into hydroxamate occurred, respectively.

From recent decades, diazo compounds have been widely employed as an efficient reagent in numerous organic transformations.[1] For instance, they could be applied for constructing cyclopropane skeletons by transferring a carbene unit to a double bond with specific diasteroselectivity.[2] Moreover, diazo compounds could also be involved in transition metal catalysed carbene transfer reactions, which resulted in the development of various strategies for the construction of new C–C and C–X (X = N, O, S, Se, Si, Sn, Ge) bonds.[3]

Recently, visible light mediated transformations of donor/acceptor diazo compounds have been intensively studied.[4] Until now, under visible light irradiation conditions, the conversion of donor/acceptor diazo compounds is mainly applied for cyclopropanation,[5] insertion reaction of X–H (X = B, C, O, N, Si, S) bond[6,7] *via* the formation of free carbene as an important intermediate, and some conversion that involves the formation of ylide intermediates.[8,9] In 2018, Davies and Jurberg first revealed that aryldiazoacetates had absorption in the visible light region (λ = 400–500 nm).[10] They found that aryldiazoacetates could occur cyclopropanation with styrene,[10] O–H insertion reactions with oxime,[6d] N–H insertion reactions with amines and C–H insertion reactions with cyclic alkanes or arenes (Scheme 1a). Subsequently, Guo and Qiu reported a visible light promoted S–H insertion reaction of aryl diazoacetates and cysteine residues in batch and flow (Scheme 1b).[11] Afterwards, photochemical multicomponent reactions involving aryldiazoacetates have been developed successively.[12]

As our research interests on the development of photochemical insertion reactions of X–H-containing molecules into aryl diazoacetates, herein we report a visible-light-promoted N–H functionalization of O-substituted hydroxamates with aryldiazoacetates. It was found that when THF was the reaction solvent, a three-component coupling product was obtained, while when 1,4-dioxane was used as the solvent, an N–H insertion product was achieved (Scheme 1c). As a multicomponent-reaction between hydroxamic acid and diazo esters has been developed,[13] this work will be a good supplement to the photochemical transformation of diazo compounds through the formation of free carbene as a key intermediate.

At the outset, we evaluated the reaction using methyl 2-diazo-2-phenylacetate **1a** and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** as the model substrates. Initially, under the irradiation of 30 W blue LEDs, the reaction was conducted in THF in the presence of $NaHCO_3$ (Table 1, entry 1), but only trace amount of product **3aa** was observed. Next, some stronger bases were employed in the reaction system. To our



Scheme 1 Visible light induced carbene insertion reaction of diazo compounds.

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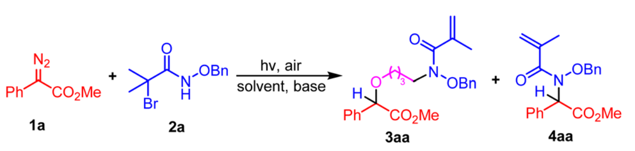
Table 1 Optimization of reaction conditions[a]



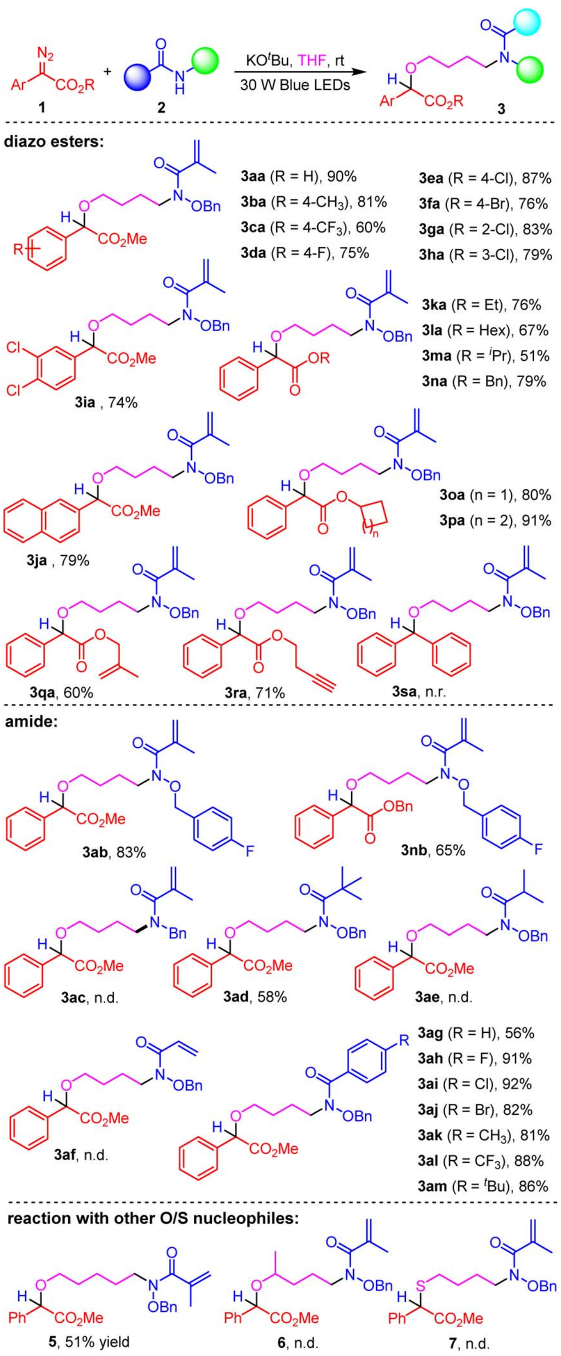
Entry	Base	Solvent	Yield[b] (%) 3aa	4aa
1	$NaHCO_3$	THF	Trace	n.d.
2	NaOH	THF	63	n.d.
3	DBU	THF	50	n.d.
4	KO^tBu	THF	90	Trace
5[c]	KO^tBu	THF	n.d.	n.d.
6	KO^tBu	1,4-Dioxane	n.d.	60
7	Cs_2CO_3	1,4-Dioxane	n.d.	49
8	NaOH	1,4-Dioxane	n.d.	43
9	$NaHCO_3$	1,4-Dioxane	n.d.	Trace
10	KO^tBu	DCE	n.d.	n.d.
11	KO^tBu	DMF	n.d.	n.d.
12	KO^tBu	CH_3CN	n.d.	n.d.
13[c]	KO^tBu	1,4-Dioxane	n.d.	n.d.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv.), base (1.2 equiv.), solvent (2 mL), 14 h, room temperature, 30 W blue LEDs ($\lambda \approx$ 440–450 nm). [b] Isolated yields. [c] Without light irradiation. n.d. = no desired product was detected.

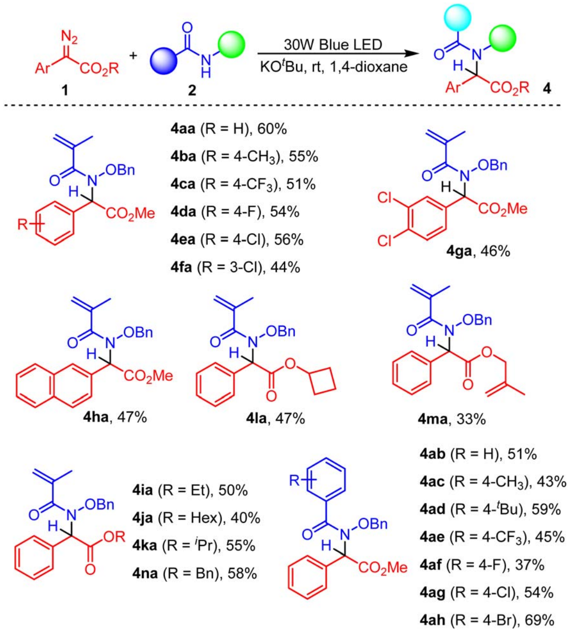
delight, the THF incorporated product methyl (*R*)-2-(4-(*N*-(benzyloxy)methacrylamido)butoxy)-2-phenylacetate **3aa** could be isolated in good yields (Table 1, entries 2–4). Especially, when KO^tBu was taken as the base, product **3aa** could be isolated in 90% yield (Table 1, entry 4). Characterization of product **3aa** by ^{1}H NMR, ^{13}C NMR and HRMS indicated that an intramolecular elimination of one molecular HBr occurred. Furthermore, control experiment under dark conditions was conducted, the result of which demonstrated the necessity of visible light irradiation condition (Table 1, entry 5). The impact of water on this transformation was studied, when 1.0 equiv. of water was added into the reaction system, except for product **3aa** (28% yield), an N–H insertion product **10** that still brominated was generated in 46% yield. (For the details of the conditional optimization, please see the ESI, Page S3 and S4.†)

Interestingly enough, N–H insertion product methyl (*R*)-2-(*N*-(benzyloxy)methacrylamido)-2-phenylacetate **4aa** was produced in 60% yield when 1,4-dioxane was employed as the solvent (Table 1, entry 6). Further exploration of different kinds of bases including Cs_2CO_3, NaOH and $NaHCO_3$ didn't bring better results (Table 1, entries 7–9). Inferior results were observed when the reaction solvent was changed to DCE, DMF or CH_3CN (Table 1, entries 10–12). Control experiment was also performed, the result showed that visible light irradiation was necessary for the generation of product **4aa** (Table 1, entry 13).

With the optimal reaction conditions in hand, we started to explore the substrate scope of the solvent-controlled N–H functionalization reaction of hydroxamates **2** with aryl diazoacetates **1**. The results are shown in Schemes 2 and 3. Scheme 2 presented the three-component reaction of aryl diazoacetates **1**, hydroxamates **2** and THF. Methyl 2-diazo-2-phenylacetate with both electron-donating and electron-withdrawing groups like Me, CF_3, F, Cl, Br at the *ortho*-, *meta*-, *para*-position of the benzene ring were all tolerated, resulting in the formation of products **3aa–3ia** in good to excellent yields. For instance, the three-component reaction of methyl 2-(4-chlorophenyl)-2-diazoacetate, *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a**



Scheme 2 Substrate scope with THF as the solvent. Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), KO^tBu (0.24 mmol), THF (2 mL), r.t., 30 W blue LEDs ($\lambda \approx$ 440–450 nm), 14 h. Isolated yield. n.d. = no desired product was detected. n.r. = no reaction.



Scheme 3 Substrate scope with 1,4-dioxane as the solvent. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), KO^{t}Bu (0.24 mmol), 1,4-dioxane (2 mL), r.t., 30W blue LEDs ($\lambda \approx$ 440–450 nm), 14 h. Isolated yield.

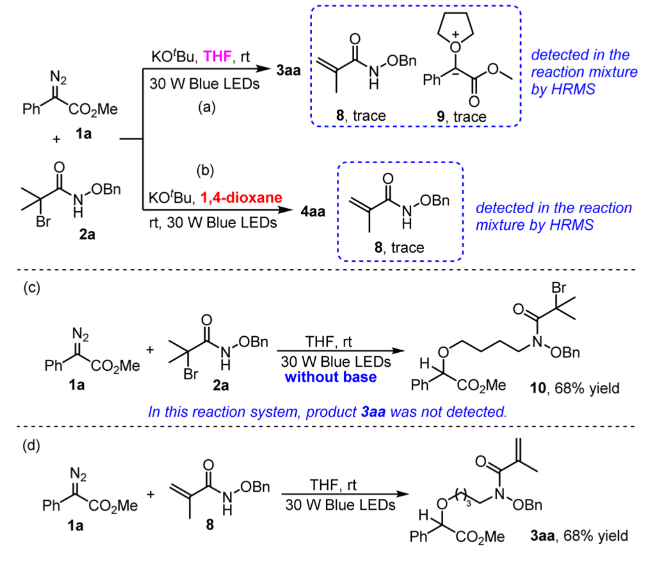
and THF gave rise to the product **3ea** in 87% yield. Additionally, the naphthyl-containing substrate **1j** was also compatible with this protocol, generating the corresponding product **3ja** in 79% yield. Subsequently, substituent modification of the ester group in aryl diazoacetates was investigated. The results showed that the replacement of methyl group with ethyl, *n*-hexyl, isopropyl, benzyl, cycloalkyl and other sensitive functional groups (**1q** and **1r**) was feasible, leading to the corresponding products **3ka–3ra** in good yields (51–91%). Unfortunately, the α-aryl diazo substrate **1s** was failed to react with **2a** and THF.

Then, we investigated the substrate scope of amide **2**. The fluoro-group containing **2b** was found to react with **1a** or **1n** smoothly, giving the corresponding products **3ab** and **3nb** in good yields. However, changing the OBn group to Bn group, no desired product **3ac** was detected. To our delight, the *tert*-butyl substituted amide **2d** worked well to produce product **3ad** in 58% yield. Unfortunately, when *N*-(benzyloxy)isobutyramide **2e** or *N*-(benzyloxy)-2-bromopropanamide **2f** were taken as the substrate, both of the reaction were failed, no desired products (**3ae**, **3af**) was observed. Additionally, aromatic amides bearing either electron-withdrawing or electron-donating groups were also tolerated, resulting in the formation of the corresponding products **3ag–3am** in good yields. Moreover, using tetrahydropyran as the reaction solvent, the corresponding product **5** was isolated in 51% yield. But, when 2-methyltetrahydrofuran or tetrahydrothiophene were taken as the reaction solvent, reactions were failed.

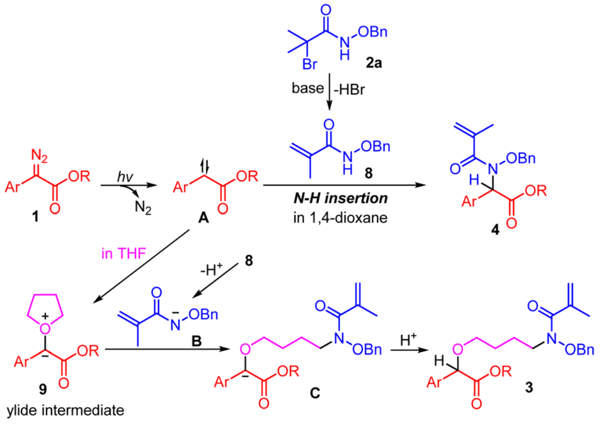
We further expanded the reaction scope of aryl diazoacetates **1** and hydroxamates **2** in 1,4-dioxane (Scheme 3). It was found that the incorporation of both electron-donating and electron-withdrawing groups on the phenyl ring of aryl diazoacetates generally afforded the corresponding N–H insertion product in 44–60% yields (Scheme 3, **4aa–4ga**). In addition, the reaction of methyl 2-diazo-2-(naphthalen-2-yl)acetate **1h** and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** also proceeded very well under the standard conditions, giving rise to **4ha** in 47% yield. Moreover, a series of aryl diazoacetates were also demonstrated to react with **2a** smoothly, leading to the formation of products **4la–4na**. As expected, various amides **2** reacted with methyl 2-diazo-2-phenylacetate **1a** successfully, giving rise to the corresponding products **4ab–4ah** in moderate yields. Different functional groups including F, Cl, Br, CF$_3$, Me, ^{t}Bu were all tolerated under the reaction conditions.

As is shown in Scheme 4, a key intermediate **8** which was generated from an intramolecular elimination reaction of substrate **2a** was detected in the reaction mixture (both in THF and 1,4-dioxane) by HRMS. Additionally, in the THF reaction system, the ylide intermediate **9** was also detected by HRMS (Scheme 4a). When we performed the reaction of **1a** and **2a** in the absence of base (Scheme 4c), it was found that the N–H insertion reaction still worked but without *in situ* dehydrobromination occurring, product **10** could be obtained in 68% yield, while in this reaction system product **3aa** could not be detected. Then, we prepared *N*-(benzyloxy)methacrylamide **8** as the substrate, and under the irradiation with 30 W blue LEDs we conducted the reaction of **8** with **1a** in THF which resulted in the formation of product **3aa** in 68% yield (Scheme 4d).

Based on the results of control experiments and previous reports,[12] a plausible mechanism for this transformation is illustrated in Scheme 5. Initially, in the presence of base, *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** was transformed into intermediate **8** through elimination of one molecular HBr. In the meantime, with the release of molecule nitrogen, a carbene intermediate **A** was generated from aryl diazoacetates **1** upon the irradiation with blue LEDs.[4–6] When the reaction was performed in 1,4-dioxane, trapping of the carbene species **A** by



Scheme 4 Mechanistic studies.



Scheme 5 Possible reaction mechanism.

the intramolecular elimination product **8** afforded the N–H insertion product **4**. However, when THF was employed as the reaction solvent, an active oxonium ylide intermediate **9** would be generated. Then, intermolecular nucleophilic attack of the nitrogen anion **B** on the intermediate **9** would lead to the formation of intermediate **C**, which further delivered the final product **3**.

Conclusions

In summary, a visible light promoted N–H functionalization of O-substituted hydroxamic acids with diazo esters under mild conditions was developed. The reactions proceeded efficiently to afford two series of N–H functionalized products of O-substituted hydroxamic acids in moderate to excellent yields with good functional group compatibility. When 1,4-dioxane was applied as the solvent, N–H insertion of the photo-generated free carbene species into hydroxamic acid derivatives occurred directly. While, when the reaction was performed in THF, it was found that THF can participate in the reaction system through a formation of an active oxonium ylide intermediate. Taken THF as a covalent linker, this strategy can be applied in medicinal chemistry to providing a new approach for antibody-drug conjugation.[14]

Conflicts of interest

There are no conflicts to declare.

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