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1,3-Dipolar [3 + 3] cycloaddition of α -halohydroxamate-based azaoxyallyl cations with hydrazonoyl chloride-derived nitrile imines†

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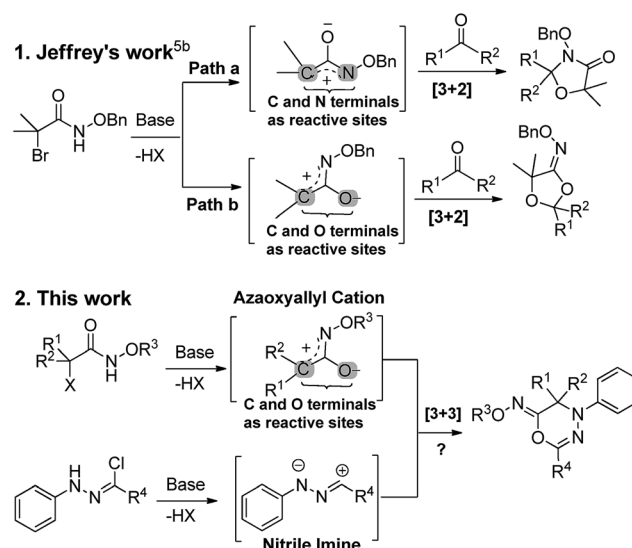
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Promoted by Et₃N, the 1,3-dipolar [3 + 3] cycloaddition of α -halohydroxamate-based azaoxyallylcations with hydrazonoyl chloride-derived nitrile imines occurred efficiently, and furnished desired products in acceptable chemical yields. The chemical structure of the title compounds was firmly confirmed by an X-ray single crystal structure analysis.

Azaoxyallylcations constitute a class of synthetically important and useful synthons, and their cycloaddition reactions serve as the main tools for the construction of structurally diverse and complex heterocycles.¹ Generally, the treatment of α -halohydroxamates with organic or inorganic bases can easily produce azaoxyallylcations. Pioneeringly, Jeffrey *et al.* reported the [4 + 3] cycloaddition of α -halohydroxamates with cyclic dienies.² Since then, the synthetic methodology of azaoxyallylcations has experienced a wide and rapid development. Similarly, the Jeffrey, Wu and Liao research groups independently devised the [3 + 2] cycloaddition of azaoxyallylcations with indole derivatives for the synthesis of pyrroloindolines.³ The Chen research group designed the [3 + 1] and [3 + 2] cycloadditions of azaoxyallylcations with sulfurylides to produce β - and γ -lactams.⁴ Moreover, the Lin, Jeffrey and Wang research groups established the [3 + 2] cycloaddition of azaoxyallylcations with aldehydes or ketones to produce oxazolidin-4-ones.⁵ Wu and co-workers envisioned the [3 + 3] cycloaddition between azaoxyallylcations and isoquinoline N-oxides.⁶ Very recently, Lin and co-workers discovered [3 + 3] cycloaddition of azaoxyallylcations with 2-alkenylindoles to prepare tetrahydro- β -carbolinones.⁷ Concerning the above-mentioned cycloaddition reactions,^{1–7} the C and N terminals of the azaoxyallylcations are involved for the bond formations (e.g., Scheme 1(1), path a). Most importantly and elegantly, Jeffrey *et al.* recently disclosed that the azaoxyallylcations could utilize their C and O terminals to couple with ketones or aldehydes (Scheme 1(1), path b).^{5b} Up to now, the

cycloaddition of azaoxyallylcations using their C and O terminals as reactive sites has rarely been investigated.⁷

Motivated by Jeffrey's work,^{5b} we first envisioned the 1,3-dipolar [3 + 3] cycloaddition of α -halohydroxamate-based azaoxyallylcations with synthetically important and useful hydrazonoylchloride-derived nitrile imines (Scheme 1(2)).⁸ Gratifyingly, we discovered that the *in situ* generated azaoxyallylcations readily utilized their C and O terminals to couple with the 1,3-dipolar nitrile imines *in situ* derived from the hydrazonoylchlorides, and produced structurally novel (*Z*)-4*H*-1,3,4-oxadiazin-6(5*H*)-imines in the acceptable chemical yields. Certainly, these new scaffolds can find some potential synthetic applications.⁹ To the best of our knowledge, such a work has not been reported in the literature to date.



Scheme 1 Representative cycloadditions involving azaoxyallylcation intermediates.

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Initially, in the presence of Et_3N , we examined the solvent effect on the [3 + 3] cycloaddition of α -halohydroxamate **1a** with hydrazonoyl chloride **2a** as shown in entries 1–6 (Table 1). Use of CH_3CN and DCM as solvents gave product **3aa** in trace amounts after 48 h (entries 4–5). In contrast, the [3 + 3] cycloaddition did not take place in toluene at all (entry 6). Choice of HFIP, TFE and EtOH as solvents generated product **3aa** in 13–60% chemical yields (entries 1–3). Basically, the protonic solvents provided better chemical yields than those obtained with the aprotic solvents (entries 1–3 vs. 4–6). Subsequently, we explored the effect of the different bases on the [3 + 3] cycloaddition in HFIP as summarized in entries 7–18. Noticeably, the used bases affected the chemical yield of the [3 + 3] cycloaddition drastically. Use of NaHCO_3 as a base delivered product **3aa** in a trace amount (entry 11). In the case of Na_2CO_3 and MeONa as bases, the [3 + 3] cycloaddition produced product **3aa** in 10% and 9% chemical yields, respectively (entries 7 & 12). In regard to the other bases tested, the chemical yield of **3aa** widely ranged from 36% to 60% (entries 8–10 & 13–18). Obviously, among all the bases tested, Et_3N behaved most efficiently, and gave product **3aa** in the highest chemical yield (entry 1). Moreover, we checked the effect of the equivalent ratio of **1a/2a**/ Et_3N on the [3 + 3] cycloaddition in the presence of Et_3N in HFIP

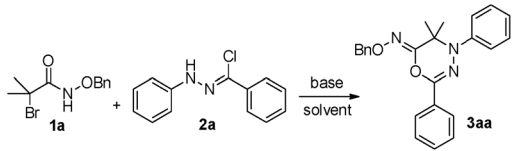
(see details in ESI[†]), and found that the ratio of 2 : 1 : 3 was the most optimal (entry 19). Finally, we attempted the [3 + 3] cycloaddition at varying reaction temperatures in 2 : 1 : 3 ratio of **1a/2a**/ Et_3N in HFIP, and found that the chemical yield of product **3aa** did not increased as we expected (entries 20–21). Also, it should be noted that, in the [3 + 3] cycloaddition between **1a** and **2a**, the formation of major product **3aa** usually was accompanied by the formation of a very polar and inseparable mixture even under the optimal reaction conditions, and that accounted for the moderate chemical yield of **3aa**.

With the optimal reaction conditions in hand, we broaden the substrate scope of [3 + 3] cycloaddition by diversifying α -halohydroxamates **1** and hydrazonoyl chlorides **2** as outlined in Tables 2 and 3. Notably, the structural nature of substrates **1** and **2** affected the chemical yield of the [3 + 3] cycloaddition dramatically. As depicted in Table 2, the hydrazonoyl chlorides **2** (**2a–2n**) widely tolerated the variation of R^4 group in the [3 + 3] cycloaddition with α -halohydroxamate **1a**, and provided products **3** (**3aa–3an**) in the reasonable chemical yields. Generally, the substrates **2** (**2e–2h** & **2j–l**) possessing an electron-poor phenyl ring as R^4 group tended to offer products **3** (**3ae–3ah** & **3aj–3al**) in higher chemical yields; in contrast, the substrates **2** (**2b**, **2d** & **2i**) containing an electron-rich phenyl ring as R^4 group preferred to furnish products **3** (**3ab**, **3ad** & **3ai**) in lower chemical yields.

As summarized in Table 3, the [3 + 3] cycloaddition between the structurally varying α -halohydroxamates **1** (**1b–1f**) and hydrazonoyl chloride **2h** proceeded quite differently, and furnished products **3** (**3bh–3fh**) in none to excellent chemical yields. Generally, the substrates **1** (**1b** & **1d**) with a tertiary α -carbon center performed better than the substrates **1** (**1c**, **1e** and **1f**) bearing a secondary or primary α -carbon center in the [3 + 3] cycloaddition with **2h**, and yielded products **3** (**3bh** & **3dh** vs. **3ch**, **3eh** & **3fh**) in excellent chemical yields. At last, we treated the substrates **1** (**1b–1d**) featuring a tertiary or secondary α -carbon center with the substrates **2** (**2a**, **2e–2g** & **2l**) possessing a phenyl ring or an electron-poor phenyl ring as R^4 group, and the chemical yield of the [3 + 3] cycloaddition ranged from 27% to 90% (**3ba**, **3ca**, **3da**, **3bg**, **3dg**, **3be**, **3bf** & **3bl**).

Moreover, the single crystal X-ray analysis firmly confirmed the chemical structure of **3ae**, and disclosed that its 4*H*-1,3,4-oxadiazin-6(5*H*)-imine ring adopts a highly twisted conformation as illustrated in Fig. 1.¹⁰ Since the fact that the C and N or C and O terminals of azaoxyallylation can serve as reactive sites in the cycloaddition,^{5b,7} we locked the two possible nonsynchronous concerted pathway 1 and pathway 2 for the [3 + 3] cycloaddition between α -halohydroxamate **1a** and hydrazonoyl chloride **2e** by conducting the DFT calculations at B3LYP/6-31+G(d) theoretical level in gas phase¹¹ as shown in Fig. 2. Initially, upon treatment with Et_3N , **1a** provides azaoxyallylation **4**, and **2a** gives nitrile imine **5**. Subsequently, regarding pathway 1, through **TS1** with an energy barrier of 18.7 kcal mol^{−1}, **4** reacts with **5** using its C and O terminals to yield **Int1**, and then the formed **Int1** barrierlessly transforms into product **3ae** as demonstrated by the intrinsic reaction coordinate (IRC). As for pathway 2, according to **TS2** bearing an energy barrier of 24.8 kcal mol^{−1}, **4** performs the cycloaddition

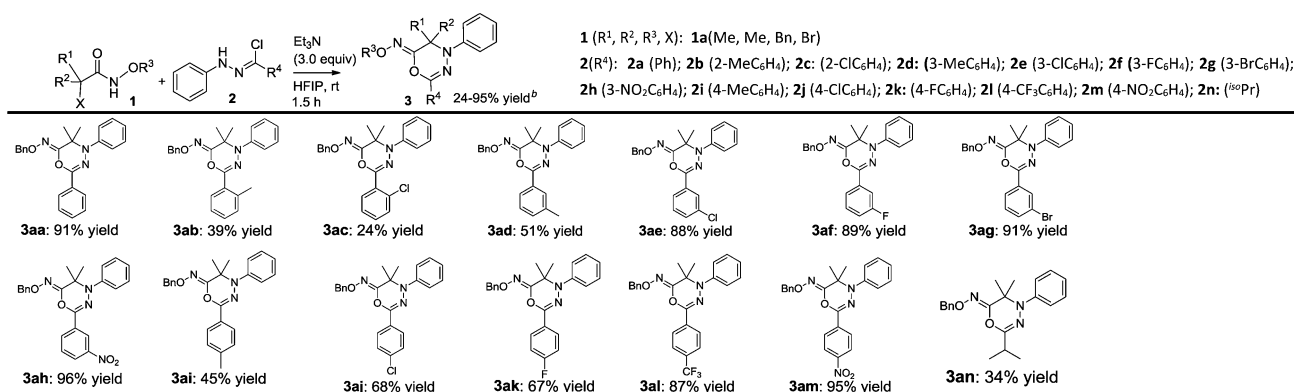
Table 1 Optimization of reaction conditions^a



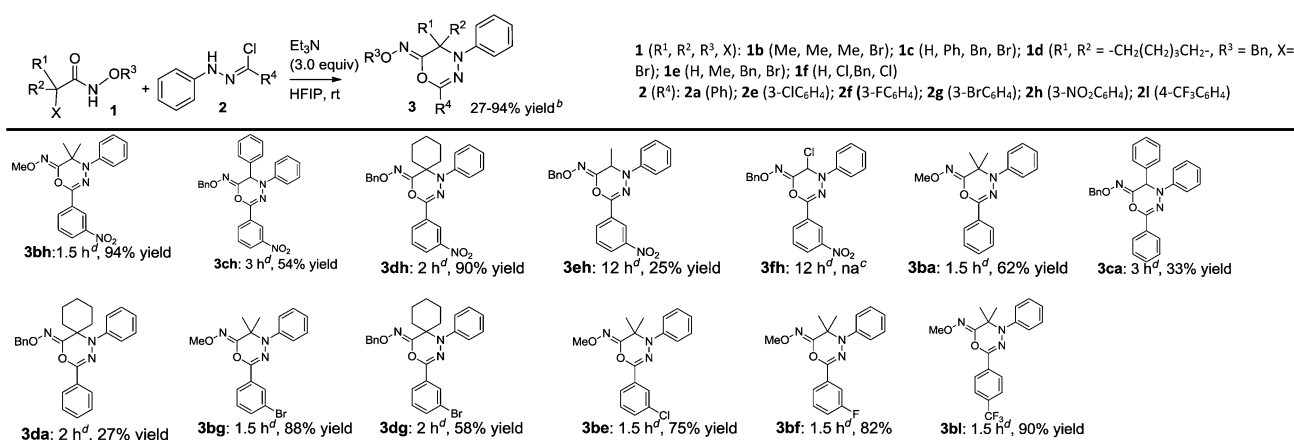
Entry	Solvent	Base	Time (h)	Yield ^b (%)
1	HFIP	Et_3N	1.5	60
2	TFE	Et_3N	48	21
3	EtOH	Et_3N	48	13
4	CH_3CN	Et_3N	48	Trace
5	DCM	Et_3N	48	Trace
6	Toluene	Et_3N	48	nr ^c
7	HFIP	Na_2CO_3	1.5	10
8	HFIP	K_2CO_3	1.5	56
9	HFIP	Cs_2CO_3	1.5	49
10	HFIP	KOH	1.5	57
11	HFIP	NaHCO_3	1.5	Trace
12	HFIP	MeONa	1.5	9
13	HFIP	DBU	1.5	56
14	HFIP	DABCO	1.5	36
15	HFIP	Quinine	1.5	50
16	HFIP	DMAP	1.5	59
17	HFIP	DIPEA	1.5	43
18	HFIP	Pyridine	1.5	39
19 ^d	HFIP	Et_3N	1.5	67
20 ^e	HFIP	Et_3N	1	53
21 ^f	HFIP	Et_3N	2	64

^a Unless otherwise noted, reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol) in the presence of base (0.25 mmol) in the specified solvent (0.5 mL) at room temperature. ^b Isolated yield. ^c No reaction. ^d In 2 : 1 : 3 ratio of **1a/2a**/ Et_3N . ^e Run at 60 °C. ^f Run at 0 °C.



Table 2 Substrate scope of hydrazonoyl chlorides^a

^a Unless otherwise noted, reactions were carried out with 0.2 mmol of **1** and 0.1 mmol of **2** in the presence of 0.3 mmol of Et₃N in 0.5 mL of HFIP at room temperature. ^b Isolated yield.

Table 3 Substrate scope of α-halohydroxamates^a

^a Unless otherwise noted, reactions were carried out with 0.2 mmol of **1** and 0.1 mmol of **2** in the presence of 0.3 mmol of Et₃N in 0.5 mL of HFIP at room temperature. ^b Isolated yield. ^c Not available. ^d Reaction time.

with **5** by employing its C and N terminals to deliver **Int2** and subsequently the generated **Int2** barrierlessly produces product **3ae'** as indicated by IRC. Overall, the pathway 1 is kinetically much more favorable than the pathway 2, and fully accounts for the formation of **3ae** in the [3 + 3] cycloaddition between **1a** and **2e**. Also, we performed the DFT calculations for the possible

pathways 1 and 2 at CPCM-B3LYP/6-311+G(d,p) level in HFIP, and found that the energy gap between **TS1** and **TS2** does not change substantially as compared with that obtained at B3LYP/6-31+G(d) theoretical level in gas phase (see details in ESI†). Certainly, the calculated energy gap between **TS1** and **TS2** is big enough to generate the observed selectivity between pathway 1 and pathway 2.¹²

In conclusion, the [3 + 3] cycloaddition of the *in situ* generated α-halohydroxamate-based azaoxyallylcations with *in situ* formed hydrazonoyl chloride-derived nitrile imines proceeded readily, and furnished the structurally novel (*Z*)-4*H*-1,3,4-oxadiazin-6(5*H*)-imines in the reasonable chemical yields. Furthermore, the exploration on the other novel cycloadditions between the α-halohydroxamate-based azaoxyallylcations and structurally diverse dipoles is ongoing in our organic lab, and will be reported in due course.

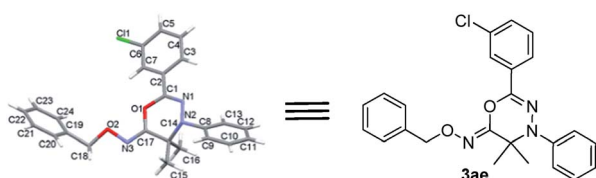


Fig. 1 X-ray single crystal structure of **3ae** (with thermal ellipsoids shown at the 50% probability level).



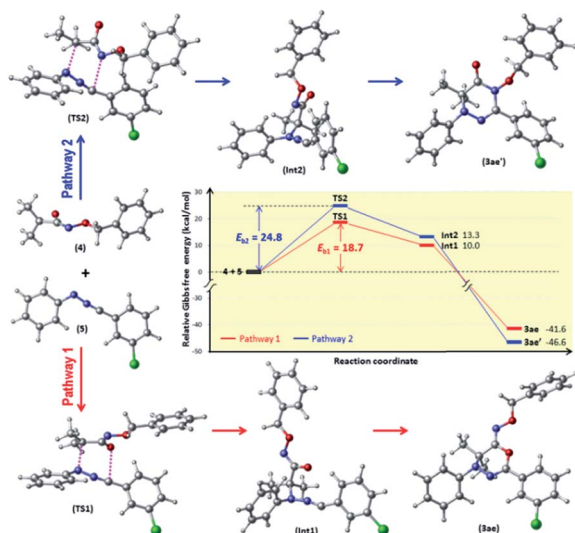


Fig. 2 The optimized geometry of all the stationary points and the energy profile for the two plausible reaction pathways of the [3 + 3] cycloaddition between **1a** and **2e** obtained at the B3LYP/6-31+G(d) theoretical level.

Conflicts of interest

There are no conflicts to declare.

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