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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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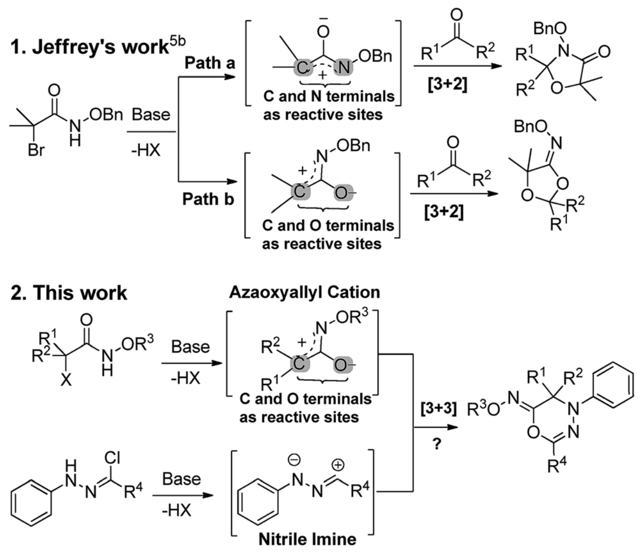
Promoted by Et_3N, the 1,3-dipolar [3 + 3] cycloaddition of α-halohydroxamate-based azaoxyallylcations with hydrazonoyl chloride-derived nitrile imines occurred efficiently, and furnished desired products in acceptable chemical yields. The chemical structure of the title compounds was firmly confirmed 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 hetereocycles.[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 cycloadditon 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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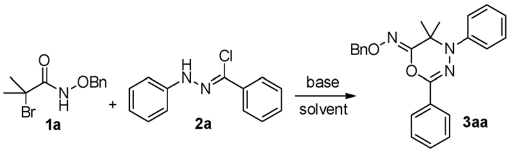
Initially, in the presence of Et_3N, we examined the solvent effect on the [3 + 3] cycloaddition of α-halohydroxamate **1a** with hydrazonoyl chloride **2a** as shown in entries 1–6 (Table 1). Use of CH_3CN and DCM as solvents gave product **3aa** in trace amounts after 48 h (entries 4–5). In contrast, 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 aprotonic 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.**

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

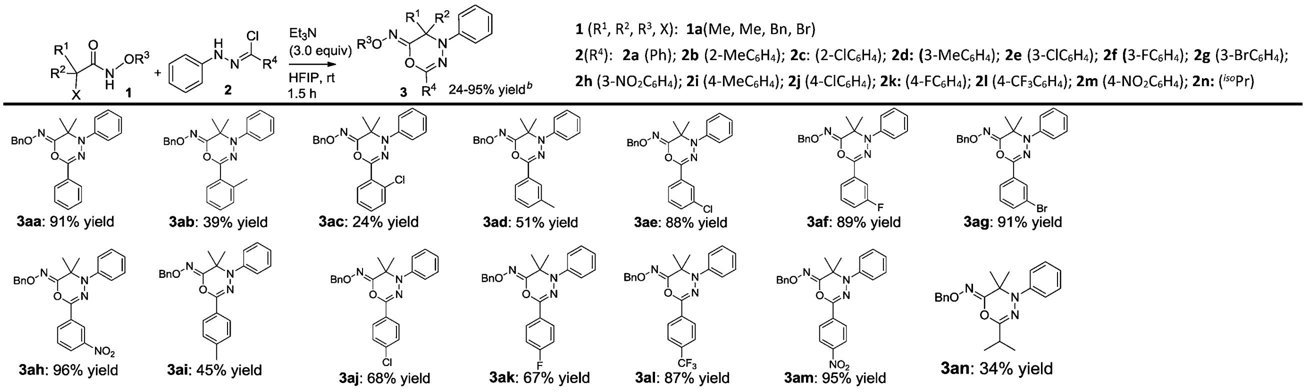
[a] Unless otherwise noted, reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol) in the presence of base (0.25 mmol) in the specified solvent (0.5 mL) at room temperature. [b] Isolated yield. [c] No reaction. [d] In 2 : 1 : 3 ratio of **1a**/**2a**/Et_3N. [e] Run at 60 °C. [f] Run at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

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 prodcuts **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 azaoxyallylcation 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 phase[11] as shown in Fig. 2. Initially, upon treatment with Et_3N, **1a** provides azaoxyallylcation **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 2 Substrate scope of hydrazonoyl chlorides[a]

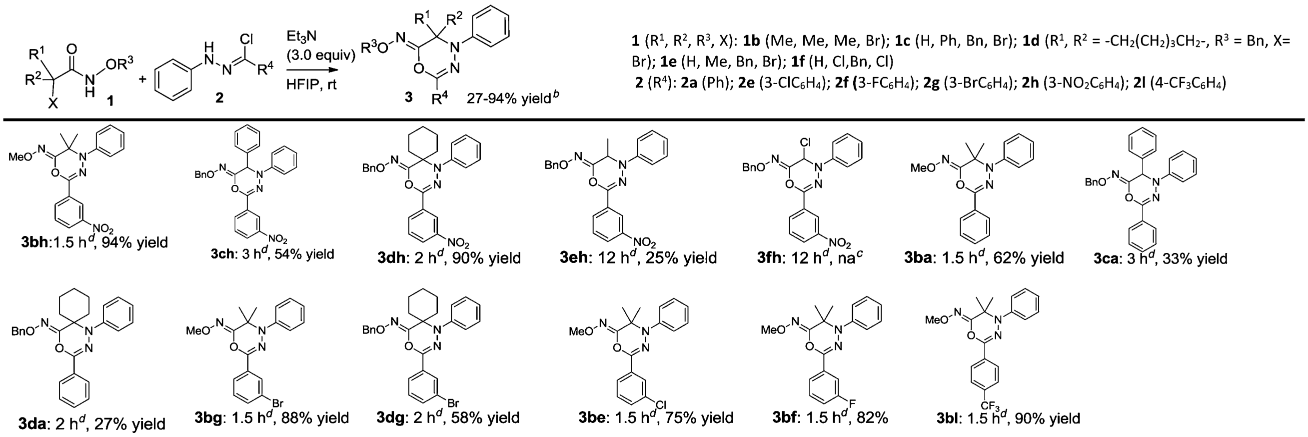


1 (R^1, R^2, R^3, X): **1a**(Me, Me, Bn, Br)
2(R^4): **2a** (Ph); **2b** (2-MeC$_6$H$_4$); **2c**: (2-ClC$_6$H$_4$); **2d**: (3-MeC$_6$H$_4$); **2e** (3-ClC$_6$H$_4$); **2f** (3-FC$_6$H$_4$); **2g** (3-BrC$_6$H$_4$); **2h** (3-NO$_2$C$_6$H$_4$); **2i** (4-MeC$_6$H$_4$); **2j** (4-ClC$_6$H$_4$); **2k**: (4-FC$_6$H$_4$); **2l** (4-CF$_3$C$_6$H$_4$); **2m** (4-NO$_2$C$_6$H$_4$); **2n**: (^{iso}Pr)

3aa: 91% yield
3ab: 39% yield
3ac: 24% yield
3ad: 51% yield
3ae: 88% yield
3af: 89% yield
3ag: 91% yield
3ah: 96% yield
3ai: 45% yield
3aj: 68% yield
3ak: 67% yield
3al: 87% yield
3am: 95% yield
3an: 34% yield

[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 Et$_3$N in 0.5 mL of HFIP at room temperature. [b] Isolated yield.

Table 3 Substrate scope of α-halohydroxamates[a]



1 (R^1, R^2, R^3, X): **1b** (Me, Me, Me, Br); **1c** (H, Ph, Bn, Br); **1d** (R^1, R^2 = -CH$_2$(CH$_2$)$_3$CH$_2$-, R^3 = Bn, X= Br); **1e** (H, Me, Bn, Br); **1f** (H, Cl,Bn, Cl)
2 (R^4): **2a** (Ph); **2e** (3-ClC$_6$H$_4$); **2f** (3-FC$_6$H$_4$); **2g** (3-BrC$_6$H$_4$); **2h** (3-NO$_2$C$_6$H$_4$); **2l** (4-CF$_3$C$_6$H$_4$)

3bh:1.5 h[d], 94% yield
3ch: 3 h[d], 54% yield
3dh: 2 h[d], 90% yield
3eh: 12 h[d], 25% yield
3fh: 12 h[d], na[c]
3ba: 1.5 h[d], 62% yield
3ca: 3 h[d], 33% yield
3da: 2 h[d], 27% yield
3bg: 1.5 h[d], 88% yield
3dg: 2 h[d], 58% yield
3be: 1.5 h[d], 75% yield
3bf: 1.5 h[d], 82%
3bl: 1.5 h[d], 90% yield

[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 Et$_3$N 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.

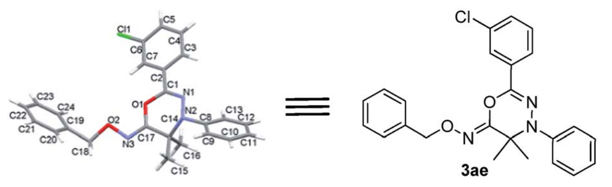


Fig. 1 X-ray single crystal structure of **3ae** (with thermal ellipsoils shown at the 50% probability level).

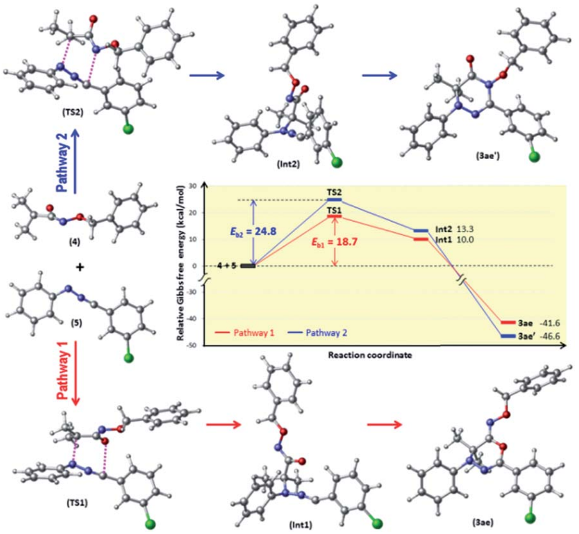


Fig. 2 The optimized geometry of all the stationary points and the energy profile for the two plausible reaction pathways of the [3 + 3] cycloaddition between **1a** and **2e** obtained at the B3LYP/6-31+G(d) theoretical level.

Conflicts of interest

There are no conflicts to declare.

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