RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2023, **13**, 24445

Intramolecular cyclization of *N*-cyano sulfoximines by N–CN bond activation†

Ye Ji Seo,‡[ab] Eunsil Kim,‡[ac] In Seok Oh,‡§[ac] Ji Young Hyun,[ab] Ji Ho Song,[ab] Hwan Jung Lim *[ab] and Seong Jun Park *[ab]

Received 23rd June 2023
Accepted 4th August 2023

DOI: 10.1039/d3ra04208a

rsc.li/rsc-advances

Metal-free halogenated anhydrides promote the intramolecular cyclization of *N*-cyano sulfoximines. Trifluoro- or trichloroacetic anhydride (TFAA or TCAA, respectively) activate the *N*-cyano groups of *N*-cyano sulfoximines, leading to the intramolecular cyclization of 2-benzamide-*N*-cyano sulfoximines **1**. This method results in excellent yields of thiadiazinone 1-oxides **2**. A full intramolecular cyclization pattern was suggested by (i) labeling experiments with ^{13}C, (ii) isolating of *N*-trifluoroacetyl sulfoximine **1ac**, and (iii) confirming the generation of the intermediate **1ad** by LC/MS analysis.

Introduction

N-Cyano sulfoximines (CN group-substituted sulfoximidoyl moieties) are readily accessible[1–6] and remarkably stable.[7] Consequently, they are widely accepted as key molecules for drug development[8–10] and crop protection (Fig. 1a).[11–13]

In addition, owing to the existence of a well-designed method for the cleavage of the N–CN bond, *N*-cyano sulfoximines have been applied as useful intermediates in the synthesis of NH sulfoximines (Fig. 1b).[1,2,7,14–16]

While transformations of *N*-cyano sulfoximines, such as [3 + 2]-cycloadditions, occur at both the carbon and nitrogen atoms of the *N*-cyano group,[17–20] acid-catalyzed hydrolysis methods have been reported for the cleaving of bonds between nitrogen and the cyano groups.[1,2,7,14–16] For hydrolysis with aqueous acids, the choice of acid influences the hydrolysis of product; thus, *N*-urea sulfoximines, a synthetic intermediate of *N*H sulfoximine, can be produced.[15,26] Furthermore, owing to its strong electrophilic properties, trifluoroacetic anhydride (TFAA) tends to react with relatively weak nucleophiles, such as nitrile groups; based on this strategy, interesting transformations have been applied in the synthesis of *N*-trifluoroacetyl sulfoximines (Fig. 1b).[24,25]

As a representative example of cyclic sulfoximines, benzothiadiazine-1-oxide derivatives, which exhibit improved pharmacological properties, showed enhanced water solubility compared to the 4-aminoquinazoline group of the reference compound Prazosin.[27] Previously, using the strategy of cleaving the N–CN bonds of *N*-cyano sulfoximines, we reported the synthesis of thiadiazine 1-oxides *via* acid-catalyzed intramolecular cyclization (Fig. 2).[26]

The highlight of our method is that it is a metal-free, one-pot reaction using an aqueous acid solution. However, despite the impressive progress made in the development of synthetic routes in recent decades, the introduction of a sulfoximinoyl moiety into a heterocyclic ring system remains challenging owing to the requirement for harsh reaction conditions, expensive transition-metal catalysts, and noncommercial amination reagents.[26,28] To establish highly efficient intramolecular cyclization under mild conditions, our study focused on the N–CN bond activation approach (Fig. 2). Specifically, chemical modifications were designed to maintain the carbon atom of the *N*-cyano groups of *N*-cyano sulfoximines in the molecular structures of the products.[29] Because of the presence of a lone pair of electrons on the nitrogen atom, the cyano group acts as a Brønsted and Lewis base.[30–34]

Results and discussion

We examined metal-free nitrile activation using various anhydrides as the electrophilic reagents. Reacting *N*-cyano sulfoximine **1a** with trichloroacetic anhydride (TCAA) and trifluoroacetic anhydride (TFAA)[24,25] in CH_2Cl_2 for 16 h at room temperature afforded the desired thiadiazinone 1-oxide **2a** in yield of 26% and 45%, respectively (entry 1, Table 1). Interestingly, compared to the trichloromethyl ($-CCl_3$) group, the trifluoromethyl ($-CF_3$) group showed an enhanced yield owing to its strong electron-withdrawing properties.[35–37] We then screened

[a]*Department of Drug Discovery, Korea Research Institute of Chemical Technology (KRICT), 141 Gajeong-ro, Yuseong-gu, Daejeon 34114, Republic of Korea. E-mail: sjunpark@krict.re.kr; Fax: +82 42 860 7160; Tel: +82 42 860 7175*

[b]*Pharmaceutical Chemistry, University of Science & Technology, Daejeon 34113, Republic of Korea*

[c]*Department of Chemistry, Sogang University, 35 Baekbeom-ro, Mapo-gu, Seoul 04107, Republic of Korea*

† Electronic supplementary information (ESI) available. CCDC 2271515. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ra04208a

‡ These authors contributed equally to this work.

§ Current address: New Drug Development Center, Daegu-Gyengbuk Medical Innovation Foundation, 80 Cheombok-ro, Dong-gu, Daegu 41061, Republic of Korea.

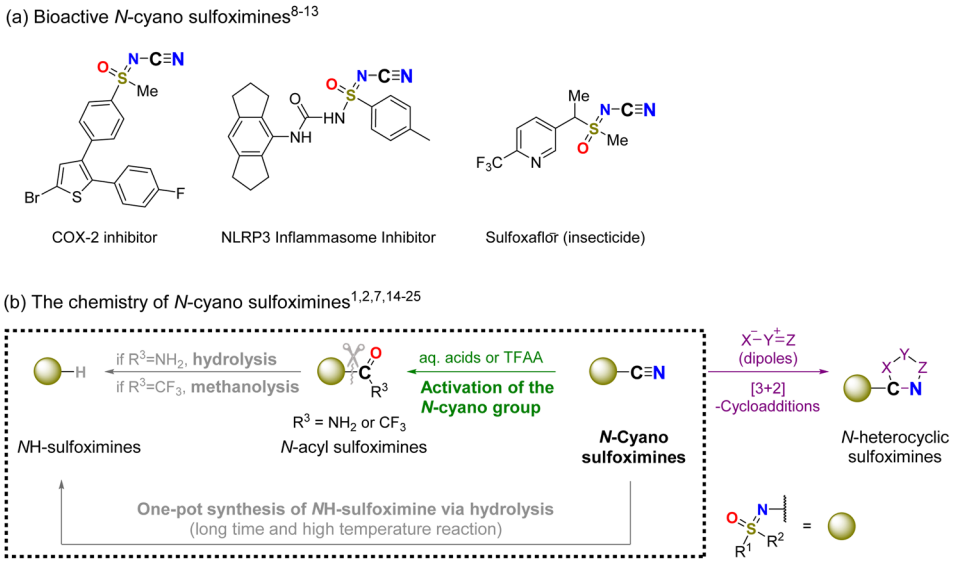


Fig. 1 (a) Bioactive *N*-cyano sulfoximes,[8–13] (b) cleavage of the *N*-cyano group under aqueous acidic conditions,[1,2,7,14–16] [3 + 2]-cycloadditions of *N*-cyano sulfoximines,[17–20] and activation of *N*-cyano group.[21–25]

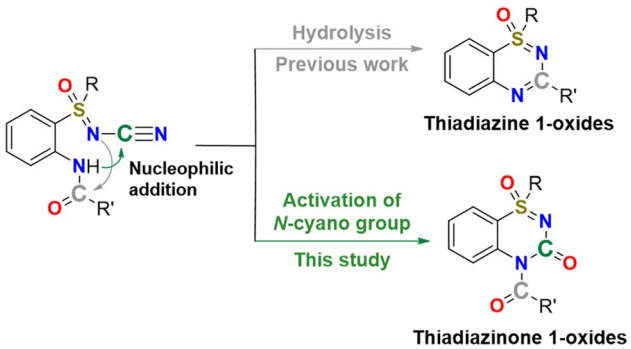
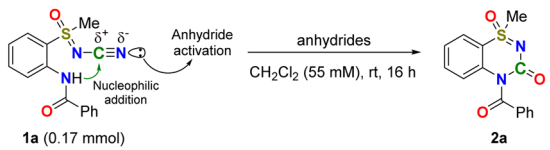


Fig. 2 Our approaches for the synthesis of thiadiazine 1-oxides[26] and thiadiazinone 1-oxides.

Table 1 Screening of amount of halogenated anhydrides

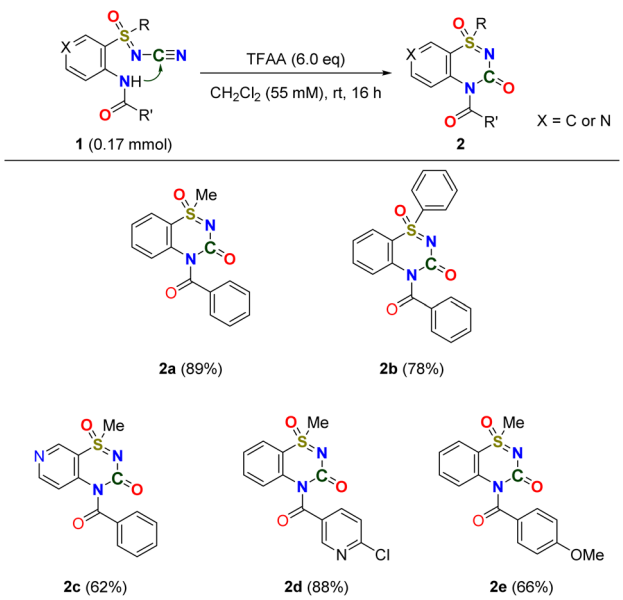


Entry	Equivalents of halogenated anhydrides	Yield[a] (**2a**, %) TFAA	TCAA
1	1	45	26
2	3	74	52
3	6	89	80

[a] After column chromatography.

the amount of anhydrides; the best result (89% yield) was obtained when 6 equiv. of TFAA was added (entry 3, Table 1). The use of other anhydrides, such as acetic, benzoic, and Boc anhydrides, was unsuccessful. Similarly, the use of trifluoromethanesulfonic anhydride (Tf_2O)[38] or methanesulfonic anhydride (Ms_2O) as the electrophilic reagent did not afford the desired **2a**. Thus, the influence of the choice of electrophilic reagent on this reaction was demonstrated. It is reasonable to assume that the relationship between electrophiles and nucleophiles, such as halogenated anhydride and nitrile, is crucial for obtaining the desired product.

The scope of the reaction was examined under optimized reaction conditions (Scheme 1). For S-methyl and S-phenyl sulfoximines, the desired benzothiadiazinone 1-oxides **2a** and **2b** were obtained in excellent yields (89% and 78%,



Scheme 1 Scope of One-pot synthesis of benzothiadiazinone 1-oxides **2**.

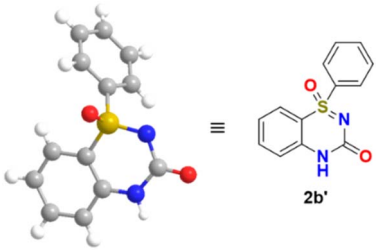


Fig. 3 X-ray crystal structures of **2b′**.[39,40]

respectively). For both heterocycle-substituted *N*-cyano sulfoximines **1c** and **1d**, the cyclized products **2c** and **2d** were obtained in excellent yields (62% and 88%). The electron-donating methoxy group in the *N*-benzamide position also provided an excellent yield, affording **2e** in 66% yield.

We report the X-ray crystal structure of thiadiazinone 1-oxide **2b′**, as shown in Fig. 3.[39,40]

We considered a mechanism involving N–CN activation, Mumm rearrangement involving O-to-N acyl group migration,[41,42] and intramolecular nucleophilic addition. It is reasonable to propose the formation of intermediate **1aa** by TFAA-promoted *N*-cyano group activation. The hypothesis involving O-to-N acyl group migration is attractive because the carbonyl group is a typical site for intramolecular nucleophilic addition.[43] This hypothesis was successfully confirmed by the generation of the intermediate **1ad** (Scheme 2, supported by LC/MS analysis experiments).[44] The results of our study on *N*-acylated sulfoximine **1ac**, which was unreactive, isolable, and very stable, clearly support the proposed mechanism of intramolecular cyclization.[45]

The kinetics of nitrile activation using halogenated anhydrides were monitored using time-resolved NMR spectroscopy. The spectra, recorded during the reaction of **1a** with TFAA for 1 h, is illustrated in ESI.† By plotting the integral value of the S-methyl peak of the desired product **2a** (3.57 ppm, when integral value of the TMS peak is 1), it can be observed that the concentration of **2a** rapidly increased with time when TFAA was used, whereas it remained almost unchanged when TCAA was used (Fig. 3). This experiment proves that the strongly

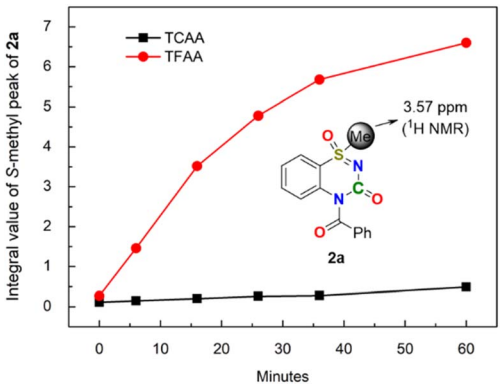
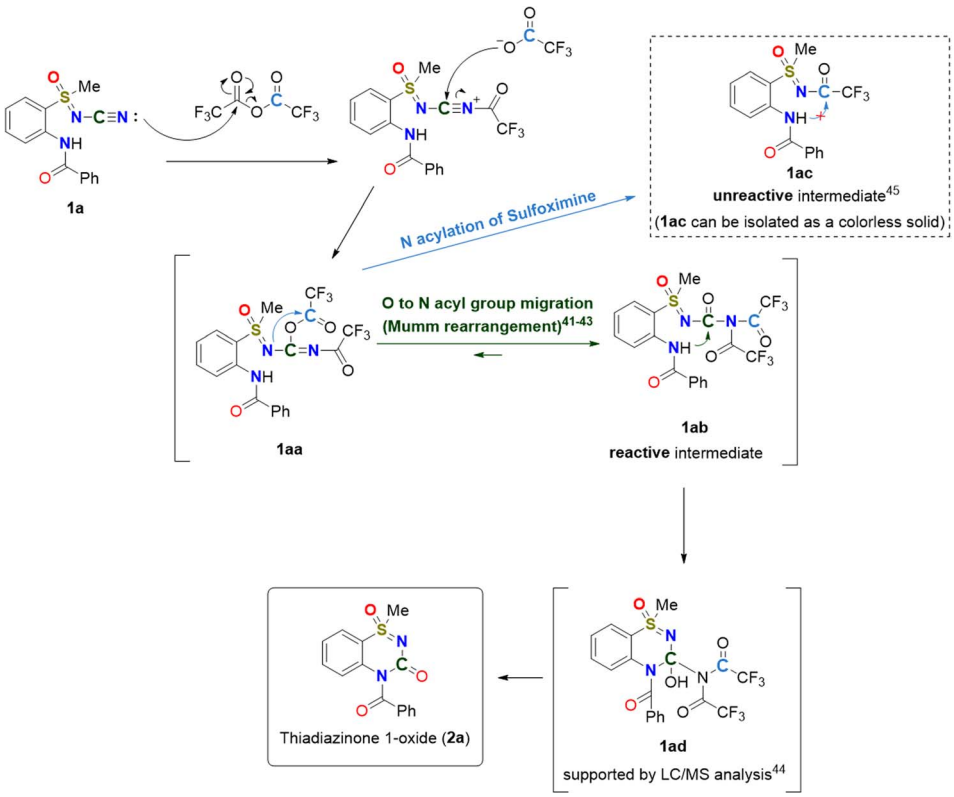
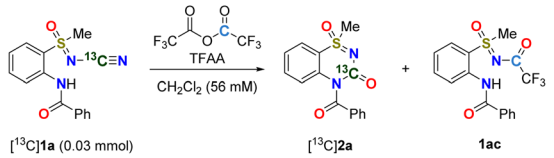


Fig. 4 ^{1}H NMR study of the metal-free nitrile activation using halogenated anhydrides.



Scheme 2 Proposed mechanism.[41–45]

Table 2 Mechanistic experiments



[13C]1a (0.03 mmol) [13C]2a 1ac

Entry	TFAA (eq.)	Reaction conditions	Yield[a] (%) [13C]2a	1ac	[13C]1a
1	6	RT, 40 min	83	—[b]	—[b]
2	6	−10 °C, 40 min	21	40	34

[a] After column chromatography. [b] Not obtained.

electrophilic TFAA readily reacts with weakly nucleophilic cyano groups (Fig. 4).

To demonstrate that the carbon atom in the resulting molecular structure was derived from the *N*-cyano group, *N*-cyano sulfoximine [^{13}C]**1a** was prepared using a ^{13}C-labeled cyanamide reagent. The reaction of *N*-cyano sulfoximine [^{13}C]**1a** with TFAA (6 equiv.) in CH_2Cl_2 for 16 h at room temperature readily afforded the desired thiadiazinone 1-oxide [^{13}C]**2a** (entry 1, Table 2). In the case of low temperatures (−10 °C), however, *N*-trifluoroacetyl sulfoxmine **1ac** was obtained (entry 2, Table 2). Regarding the mechanism (Scheme 2), compound **1ac** was formed by the *N*-acylation of sulfoximine with TFAA. Importantly, this hypothesis was supported by the experimental results.

Conclusions

In summary, we have developed a method for the anhydride-promoted intramolecular cyclization of *N*-cyano sulfoximines. Transition metal catalysts or harsh reaction conditions were not required. We believe that we have identified a clear mechanistic pathway for the activation of the *N*-cyano groups of *N*-cyano sulfoximines *via* the addition of commercially available halogenated anhydrides. We demonstrated the intramolecular cyclization of *N*-cyano sulfoximines to prepare an important class of sulfoximidoyl heterocycles, thiadiazinone 1-oxides **2**, in excellent yields. It is predicted by the KRICT AI platform that thiadiazinone 1-oxides **2** will exhibit excellent drug-like properties with low toxicities (in detail, please see the ESI†).[46–52] Current efforts by our group are directed toward the further application of these attractive molecules for drug discovery.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by the Korea Drug Development Fund funded by Ministry of Science and ICT, Ministry of Trade, Industry and Energy, and Ministry of Health and Welfare (HN21C1078, Republic of Korea) and by KRICT (KK2331-30 and SI2231-30).

Notes and references

1 P. Stoss and G. Satzinger, *Tetrahedron Lett.*, 1973, **14**, 267–268.
2 O. Garciá Mancheño, O. Bistri and C. Bolm, *Org. Lett.*, 2007, **9**, 3809–3811.
3 A. Pandey and C. Bolm, *Synthesis*, 2010, 2922–2925.
4 P. Cutler, R. Slater, A. J. F. Edmunds, P. Maienfirsch, R. G. Hall, F. G. P. Earley, T. Pitterna, S. Pal, V.-L. Paul, J. Goodchild, M. Blacker, L. Hagmann and A. J. Crossthwaite, *Pest Manage. Sci.*, 2013, **69**, 607–619.
5 F. Teng, J.-T. Yu, Y. Jiang, H. Yang and J. Cheng, *Chem. Commun.*, 2014, **50**, 8412–8415.
6 C. A. Dannenberg, L. Fritze, F. Krauskopf and C. Bolm, *Org. Biomol. Chem.*, 2017, **15**, 1086–1090.
7 S. Wiezorek, P. Lammers and C. Bolm, *Chem. Soc. Rev.*, 2019, **48**, 5408–5423.
8 S. J. Park, H. Baars, S. Mersmann, H. Buschmann, J. M. Baron, P. M. Amann, K. Czaja, H. Hollert, K. Bluhm, R. Redelstein and C. Bolm, *ChemMedChem*, 2013, **8**, 217–220.
9 A.-D. Steinkamp, N. Seling, S. Lee, E. Boedtkjer and C. Bolm, *MedChemComm*, 2015, **6**, 2163–2169.
10 S. Agarwal, S. Sasane, H. A. Shah, J. P. Pethani, P. Deshmukh, V. Vyas, P. Iyer, H. Bhavsar, K. Viswanathan, D. Bandyopadhyay, P. Giri, J. Mahapatra, A. Chatterjee, M. R. Jain and R. Sharma, *ACS Med. Chem. Lett.*, 2020, **11**, 414–418.
11 Y. Zhu, M. R. Loso, G. B. Watson, T. C. Sparks, R. B. Rogers, J. X. Huang, B. C. Gerwick, J. M. Babcock, D. Kelly, V. B. Hedge, B. M. Nugent, J. M. Renga, I. Denholm, K. Gorman, G. J. DeBoer, J. Hasler, T. Meade and J. D. Thomas, *J. Agric. Food Chem.*, 2011, **59**, 2950–2957.
12 J. M. Babcock, C. B. Gerwick, J. X. Huang, M. R. Loso, G. Nakamura, S. P. Nolting, R. B. Rogers, T. C. Sparks, J. Thomas, G. B. Watson and Y. Zhu, *Pest Manage. Sci.*, 2011, **67**, 328–334.
13 G. B. Watson, M. R. Loso, J. M. Babcock, J. M. Hasler, T. J. Letherer, C. D. Young, Y. Zhu, J. E. Casida and T. C. Sparks, *Insect Biochem. Mol. Biol.*, 2011, **41**, 432–439.
14 V. B. Pandya and P. R. Patel, Cadila Healthcare Limited. WO2009053999A2, 2009.
15 O. G. Mancheño, J. Dallimore, A. Plant and C. Bolm, *Adv. Synth. Catal.*, 2010, **352**, 309.
16 S. J. Park, PhD thesis, RWTH Aachen University, Aachen, Germany, 2013.
17 O. G. Mancheño and C. Bolm, *Org. Lett.*, 2007, **9**, 2951–2954.
18 S. Kim, J. E. Kim, J. Lee and P. H. Lee, *Adv. Synth. Catal.*, 2015, **357**, 3707–3717.
19 M. L. C. Reddy, F. R. N. Kahn and V. Saravanan, *Org. Biomol. Chem.*, 2019, **17**, 9187–9199.
20 F. Krauskopf, K.-N. Truong, K. Rissanen and C. Bolm, *Eur. J. Org. Chem.*, 2020, 2761–2765.
21 T. Mukaiyama, S. Ohishi and H. Takamura, *Bull. Chem. Soc. Jpn.*, 1954, **27**, 416–421.

22 P. Stoss and G. Satzinger, *Tetrahedron Lett.*, 1973, **14**, 267–268.
23 O. G. Mancheño, J. Dallimore, A. Plant and C. Bolm, *Adv. Synth. Catal.*, 2010, **352**, 309–316.
24 O. G. Mancheño, O. Bistri and C. Bolm, *Org. Lett.*, 2007, **9**, 3809–3811.
25 T. A. Khan, J. D. Scott and J. N. Cumming, WO2014150331A1, 2014.
26 I. S. Oh, Y. J. Seo, J. Y. Hyun, H. J. Lim, D. –H. Lee and S. J. Park, *ACS Omega*, 2022, **7**, 2160–2169.
27 R. D. Dillard, T. T. Yen, P. Stark and D. E. Pavey, *J. Med. Chem.*, 1980, **23**, 717–722.
28 C. Wu, R. Huang, M. Zhang and Z. Chen, *J. Org. Chem.*, 2020, **85**, 841–850.
29 Y. Xia, H. Jiang and W. Wu, *Eur. J. Org. Chem.*, 2021, 6658–6669.
30 S. P. Larissa, I. F. S. Marra and G. W. Amarante, *Quim. Nova*, 2022, **45**, 712–727.
31 Note that a Lewis acid promoted intramolecular cyclization of *N*-cyano sulfoximine was unsuccessful. The combination of *N*-cyanosulfoximine **1a** with various Lewis acid additives, such as $ZnBr_2$, $SnCl_4$, and $B(C_6F_5)_3$,[32,33] (each 3 equiv.) in toluene for 16 h at 90 °C did not produce the desired thiadiazinone 1-oxide **2a**. These results may be related to the weak nucleophilicity of nitrile group due to the strong electron-withdrawing ability of *N*-cyano sulfoximine group.[34]
32 U. P. Saikia, G. Borah and P. Pahari, *Eur. J. Org. Chem.*, 2018, 1211–1217.
33 V. D. Cerón, L. A. Illicachi and B. Insuasty, *Molecules*, 2023, **28**, 257.
34 U. Lücking, *Angew. Chem., Int. Ed.*, 2023, **52**, 9399–9408.
35 G. A. Olah, R. D. Chambers and G. K. S. Prakash, *Synthetic Fluorine Chemistry*, Wiley, New York, 1992.
36 M. Schlosser, *Angew. Chem., Int. Ed.*, 1998, **37**, 1496.
37 G. A. Olah, G. K. S. Prakash, A. Molnar and J. Sommer, *Superacid Chemistry*, Wiley, New York, 2nd edn, 2009.
38 Q. Qin, Z. Cheng and N. Jiao, *Angew. Chem., Int. Ed.*, 2023, **62**, e202215008.
39 Crystallization of **2b** from different solvents, such as MeOH, toluene, and *n*-hexane, has been performed with evaporative crystallization, and it produced the dibenzoyl crystalized product **2b′**.
40 CCDC 2271515 (**2b′**) contain the supplementary crystallographic data for this paper. These data are provided free of by The Cambridge Crystallographic Centre.
41 O. Mumm, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 886–893.
42 O. Mumm, H. Hesse and H. Volquartz, *Ber. Dtsch. Chem. Ges.*, 1915, **48**, 379–391.
43 W. P. Norris, L. H. Merwin and G. S. Ostrom, *J. Org. Chem.*, 1997, **62**, 9070–9075.
44 For the identification of reaction intermediate, we have used LC/MS analysis. Under the finetuned reaction condition, the reaction mixture was aliquoted in small portion. And then the aliquoted reaction mixture was analyzed by LC/MS. According to the LC/MS results, we could find the exact mass of fragments of intermediate **1ad**. In detail, please see the ESI.†
45 The intramolecular cyclization reactions of **1ac** using various reaction conditions were unsuccessful. In detail, please see the ESI.†
46 For cardiotoxicity: J. Y. Ryu, M. Y. Lee, J. H. Lee, B. H. Lee and K.-S. Oh, *Bioinformatics*, 2020, **36**, 3049–3055.
47 For BBB permeability: B. Shaker, M.-S. Yu, J. S. Song, S. Ahn, J. Y. Ryu, K.-S. Oh and D. Na, *Bioinformatics*, 2021, **37**, 1135–1139.
48 For cardiotoxicity v2.0: H.-M. Lee, M.-S. Yu, S. R. Kazmi, S. Y. Oh, K.-H. Rhee, M.-A. Bae, B. H. Lee, D.-S. Shin, K.-S. Oh, H. Cheong, D. Lee and D. Na, *BMC Bioinf.*, 2019, **20**, 68–80.
49 For metabolic stability: J. Y. Ryu, J. H. Lee, B. H. Lee, J. S. Song, S. Ahn and K.-S. Oh, *Bioinformatics*, 2022, **38**, 364–368.
50 For hepatotoxicity: J. Lee, M.-S. Yu and D. Na, *Curr. Bioinf.*, 2022, **17**, 296–303.
51 For reproductive toxicity: M.-S. Yu, J. Lee, Y. Lee and D. Na, *BMC Bioinf.*, 2020, **245**, 2–8.
52 For PredAOT: J. Y. Ryu, W. D. Jang, J. Jang and K.-S. Oh, *BMC Bioinf.*, 2023, **24**, 2–10.