OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

[3 + 2]-Annulation of Azaoxyallyl Cations and Thiocarbonyls for the Assembly of Thiazolidin-4-ones

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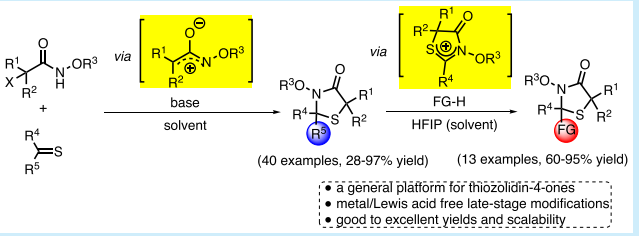
Supporting Information

ABSTRACT: A base-promoted, efficient [3 + 2] annulation between azaoxyallyl cations and thiocarbonyls is reported for flexible access to highly functionalized thiazolidin-4-one derivatives in good to excellent yields. An intriguing feature of this method is the metal or Lewis acid free late-stage entry of distinct set of functional groups at C2 of thiazolidin-4-ones via substitution of a latent amino functional group. Overall, this approach constitutes a general platform for convenient access to this medicinally important scaffold.

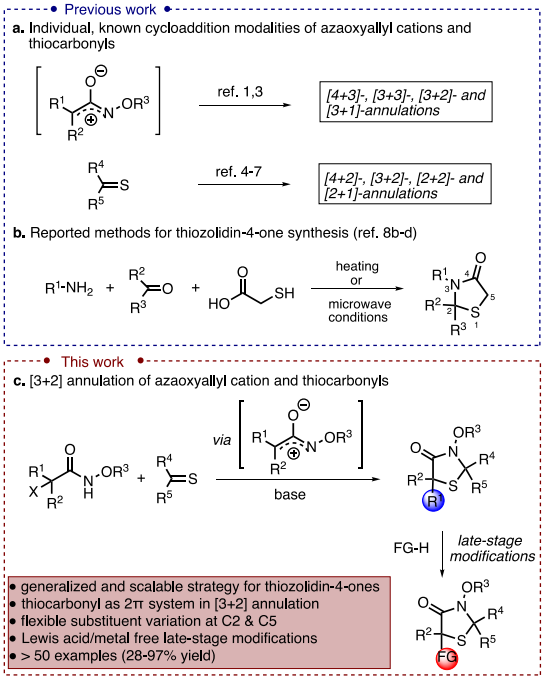


Azaoxyallyl cation, a transiently formed reactive species, has been recognized as an important synthon for the construction of important nitrogen-containing heterocycles.[1−3] Formation of this species was first speculated during the hydrolysis study of α-lactams in 1968.[2] However, its existence remained experimentally elusive until 2011 when Jeffrey et al. demonstrated its trapping with cyclic dienes via a [3 + 4] cycloaddition reaction.[1b] Since then, an expedited development of different [3 + m] cycloadditions with azaoxyallyl cation have appeared in the literature from the groups of both Jeffrey and others (Scheme 1a).[1−3] Notably, a major portion of these developments is pillared on the use of different carbonyl compounds such as aldehydes, ketones, enals, etc.

While carbonyls are the widely used feedstock functional groups in organic synthesis, their heavier analogues, such as thiocarbonyls, are markedly underrepresented in the context. This can be corroborated with difficulties in handling these compounds for their highly reactive nature, which often leads to side reactions and oligomerization. Notwithstanding the obstacles, thiocarbonyls have been employed for the synthesis of various heterocycles via development of [2 + 1],[4] [2 + 2],[5] and [4 + 2][6] cycloadditions, in conjunction to some scarcely reported [3 + 2][7] annulations (Scheme 1a).

Among the sulfur-containing heterocycles, thiazolidin-4-one derivatives are of particular significance as they are featured in many medicinally relevant compounds exhibiting wide range of biological activities,[8] such as anticancer, antimicrobial, antiviral, antimycobacterial, anti-inflammatory, antipsychotic, etc. Despite the apparent importance of this scaffold, access to the diversely functionalized variants have not been a straightforward task. The most common strategy for the preparation of this heterocycle involves condensation of aldehyde, amine, and mercaptoacetic acid at high temperature or under microwave conditions.[8b−d] Apart from the use of elevated temperature, this approach has limitations such as unavailability of suitably functionalized α-mono- or disubstituted mercaptoacetic acid derivatives and the incompatibility to use ketones that combinedly impede the accessibility of thiazolidin-4-one

Scheme 1. Previous Reports and Our Approach



Received: June 5, 2019

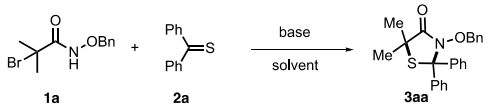
DOI: 10.1021/acs.orglett.9b01933
Org. Lett. XXXX, XXX, XXX–XXX

possessing varied substituents at C2 and C5 position (Scheme 1b).

Prompted by the serious paucity of available means to explore the chemical space around this privileged structure, we were interested in developing an efficient and versatile strategy for ready access to densely functionalized thiazolidin-4-ones. We envisaged that compatibly engaging the in situ generated azaoxyallyl cation with thiocarbonyls in [3 + 2] fashion could constitute a promising approach for their assembly. Herein, we report a successful realization of this strategy (Scheme 1c). Additionally, the potential of a latent amino functional group at C2 of the synthesized thiazolidin-4-ones was exploited for making late-stage entries of very distinct classes of functional groups, which clearly would be a highly challenging task if pursued with the pre-existing methods. Thus, the present strategy as a whole offers a unified platform for the synthesis of this particular thioheterocycle, and we expect these scaffolds to find useful applications in medicinal chemistry.

At the outset of our studies, we first checked the feasibility of the anticipated [3 + 2] annulation with α-bromo hydroxamate **1a** and thiobenzophenone **2a** as model substrates, and the screening results are summarized in Table 1. Considering the

Table 1. Optimization Studies[a]



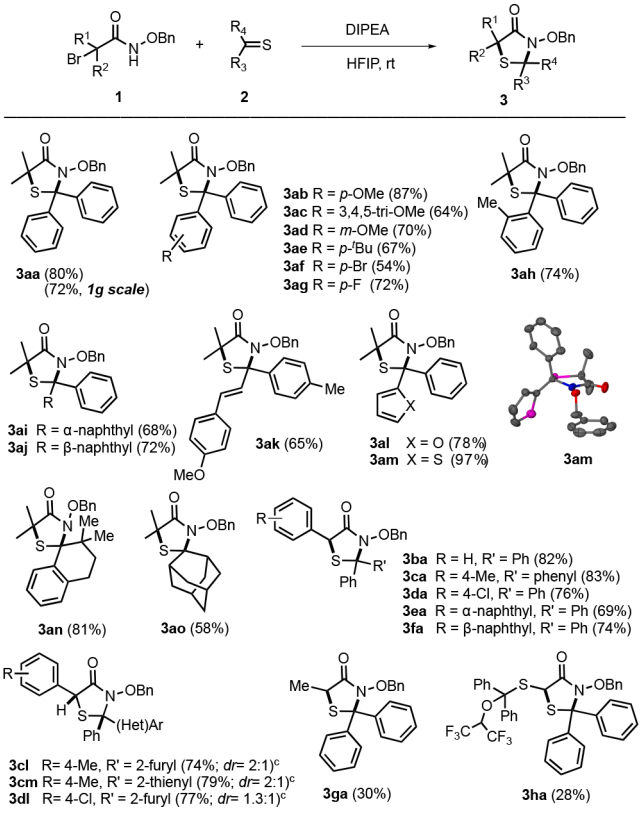
entry	base	solvent	time (h)	yield[b] (%)
1	K_2CO_3	HFIP	0.5	61
2	Na_2CO_3	HFIP	0.5	70
3	Na_2CO_3	CH_3CN	0.5	26
4	Na_2CO_3	CH_2Cl_2	0.5	15
5	Cs_2CO_3	HFIP	0.5	40
6	Et_3N	HFIP	0.5	30
7	DBU	HFIP	0.5	38
8	pyridine	HFIP	0.5	20
9	DIPA	HFIP	0.5	20
10	DIPEA	HFIP	0.5	80
11[c]	DIPEA	HFIP	1.0	45
12[d]	DIPEA	HFIP	1.0	42
13	DIPEA	TFE	0.5	30

[a]Reaction conditions: **1a** (1.0 equiv), **2a** (1.0 equiv), base (2.0 equiv), solvent (0.4 M), reaction time (0.5−1.0 h). [b]Yields of the isolated products. [c]Reaction performed at 0 °C. [d]Reaction concentration was 0.1 M.

stabilization of the putative azaoxyallyl cation by fluorinated solvents,[1b] first we chose hexafluoro-2-propanol (HFIP) for the reaction. Pleasingly, inorganic bases such as K_2CO_3 and Na_2CO_3 both furnished the desired product in good yields in HFIP (entries 1 and 2). Use of other solvents and Cs_2CO_3 as base were found to be inferior (entries 3−5). Next, different organic bases were screened in the reaction. Use of Et_3N, DBU, pyridine, and DIPA afforded moderate to low yields of the product (entries 6−9). Gratifyingly, DIPEA provided the best result and afforded **3aa** in 80% yield (entry 10). Performing this reaction at 0 °C or at a lower concentration or in TFE had detrimental effects (entries 11−13).

With the optimized conditions in hand, we next proceeded to explore the generality of the transformation with different thioketones (Scheme 2). First, electronic and steric effects of

Scheme 2. Scope for the Reaction of Thioketones with α-Halo Hydroxamates[a,b]



[a]Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), DIPEA (2.0 equiv), HFIP (0.4 M). [b]Yields of the isolated products. [c]Isolated as diastereomeric mixture; relative configuration of major diastereomer is shown.

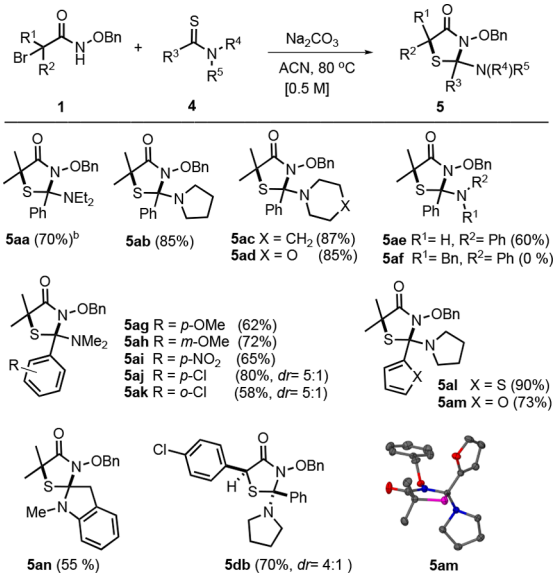
different substituents on the aromatic ring of diaryl thioketones were evaluated. In fact, the presence of both electron-donating and electron-withdrawing groups at the *ortho*, *meta*, and *para* positions smoothly afforded the desired products in good to excellent yields (**3ab**−**3ah**). Larger aromatic rings could be easily accommodated into the products (**3ai**−**3aj**) as well. Next, we evaluated a thiochalcone derivative **2k** in the reaction. This class of compounds have high propensity for dimerization and mostly participated as a 4π heterodiene system[9] in the reported cycloaddition reactions. In our case, exclusive [3 + 2] cycloadduct (**3ak**) was obtained through the C═S unit. Thiophene- and furan-containing substrates also furnished the desired products in excellent yields (**3al**−**3am**). Interestingly, in former two examples, remarkable chemoselectivity of thiocarbonyl moiety was observed, despite the fact that the rest of the groups (such as alkene or furan) are also known to react with the azaoxyallyl cation.[1b,10] Aliphatic thiocarbonyls were also used successfully in the process (**3an**, **3ao**). Importantly, the ability to use various α-aryl-substituted chlorohydroxamates in the reaction opened up the possibility to access various C5 aryl- and naphthyl-substituted (**3ba**−**3fa**, **3cl**, **3cm**, **3dl**) products. The later compounds were obtained as a mixture of diastereomers. Mono-α-substituted halohydroxamates were less efficient compared to the former examples. The presence of a single methyl group at the α-position afforded **3ga** in 30% yield. Interestingly, monochloro-substituted halohydroxamate **1h** afforded **3ha** (28%) in

DOI: 10.1021/acs.orglett.9b01933
Org. Lett. XXXX, XXX, XXX−XXX

reaction with **2a**. This can be explained on the basis of a secondary reaction that occurred via the displacement of the α-chloride by thiobenzophenone on the initially formed product. The ensuing carbocation was then captured with the HFIP addition.

With the notion of incorporating an amino substituent at the C2 position of thiazolidin-4-ones, thioamides were chosen next as another thiocarbonyl variant. We began the reaction with **1a** and *N*,*N*-diethylthiobenzamide (**4a**) under the optimized conditions (i.e., with DIPEA in HFIP), which, however, was unsuccessful for delivery of the desired product (vide infra). After some additional screening, gratifyingly, the desired product **5aa** was obtained with Na_2CO_3 in acetonitrile at 80 °C. In fact, this condition suitably worked for a range of other *N*,*N*-dialkylthiobenzamides (**5ab**−**5ad**). Secondary *N*-aryl thioamides were compatible in the process (**5ae**), whereas tertiary *N*-aryl thioamide proved futile (**5af**) (Scheme 3).

Scheme 3. Scope for the Reaction of Thioamides with α-Halo Hydroxamates[a]

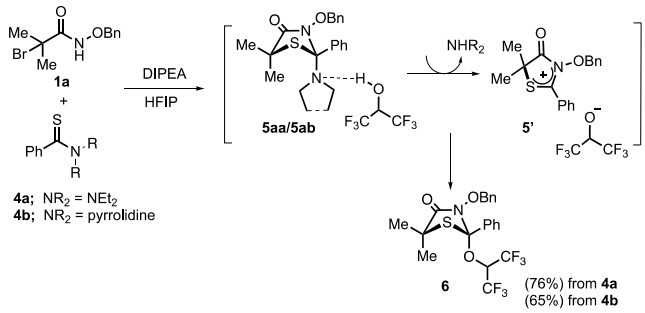


[a]Reaction conditions: **1** (2.0 equiv), **4** (1.0 equiv), base (4.0 equiv). Isolated yields are given. [b]64% yield for 1.0 g scale reaction with **4a**.

Various electron-donating and electron-withdrawing substituents on the aromatic ring of benzamides were tolerated (**5ag**−**5ak**). Substrates containing a heterocyclic nucleus (**5al**, **5am**) were used successfully, and indole-2-thione furnished spirocyclic compound **5an**. α-Aryl-substituted chlorohydroxamate also reacted with thioamide and furnished **5db**. X-ray structural analysis of **5am** revealed the axial conformational preference of the pyrrolidine moiety. Compounds **5aj**, **5ak**, and **5db** were obtained as mixture of diastereomers.[8b] It is important to note that the reaction did not proceed when α-haloamide was used in the reaction instead of α-halohydroxamate.

Curiously, when the reaction of α-bromohydroxamate **1a** and thioamide **4a** was performed in DIPEA/HFIP, both of the starting materials were consumed within 30 min and led to the formation of a new compound that differed from the expected 2-aminothiazolidin-4-one product (**5aa**). The new compound was later characterized to be an HFIP addition product **6** (76%) as supported by $^1H/^{13}C/^{19}F$ NMR and MS analysis. Interestingly, compound **6** was also obtained when **1a** was subjected to reaction with another thioamide **4b** (Scheme 4).

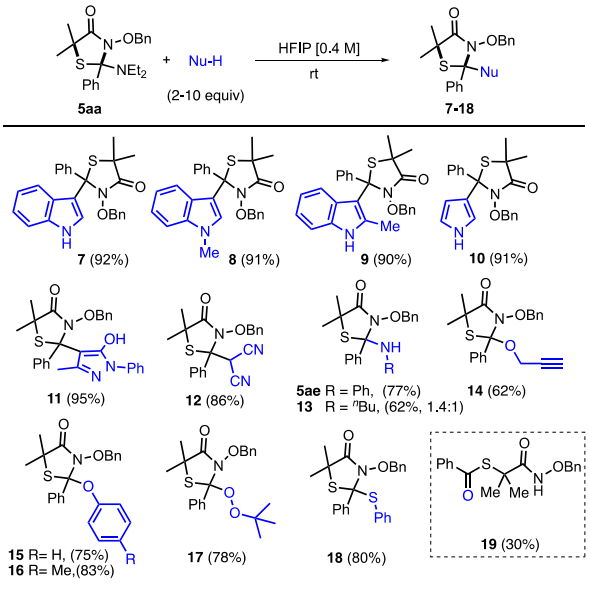
Scheme 4. Plausible Mechanism of Solvolysis of 2-Aminothiazolidin-4-ones by HFIP



This clearly indicated that both of the reactions proceeded via a common intermediate. We speculated that 2-amino-4-thiazolidinones (e.g., **5aa** and **5ab**) would have formed first in each case and subsequently were converted to **6** through rapid solvolysis by HFIP (via a putative intermediate, **5′**), as the later is a highly ionizing solvent with strong hydrogen-bond donor ability.[11] This proposition was further supported by a control experiment; when **5aa** was stirred separately in HFIP at room temperature, it was immediately converted to compound **6** (90%). ^1H NMR monitoring of this reaction revealed the rapid and quantitative conversion of **5aa** to **6**, with the release of Et_2NH in the reaction mixture (see Figure S4).

Intrigued by the above observation, we envisioned the possibility of further synthetic elaboration of **5aa** or similar compounds through incorporation of diverse set of functional groups at C2, essentially under Bronsted acid but metal free conditions (Scheme 5). In this context, we first investigated the reaction of **5aa** with a carbon nucleophile such as indole using HFIP as solvent. To our delight, the C3 addition of indole occurred smoothly at room temperature and furnished compound **7** in excellent yield (92%). Use of **5ab** instead of **5aa** worked with similar efficiency and afforded **7** in 90% yield.

Scheme 5. C-2 Modifications of 2-Aminothiazolidin-4-ones



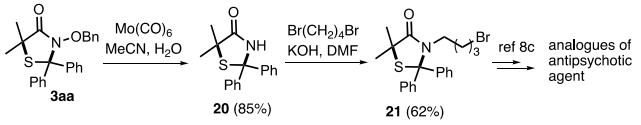
DOI: 10.1021/acs.orglett.9b01933
Org. Lett. XXXX, XXX, XXX−XXX

A *one-pot* transformation of **1a**, **4a**, and indole was also viable, albeit in lower yield (50%). Other indole derivatives and pyrrole also reacted efficiently under the conditions, affording **8**−**10** in high yields. The reaction scope can be extended to different active methylene compounds, such as pyrazolone derivative and malononitrile (**11** and **12**).

Use of heteroatom nucleophiles ranging from aromatic amines and alcohols to aliphatic variants was successful (**5ae**, **13**−**16**). Importantly, since the reaction of **5aa** with aniline or $^{n}BuNH_2$ was viable, this indicated the possibility of a strain-driven solvolysis event of the 3° amino moiety on **5aa** (or **5ab**) by HFIP, which apparently was absent for related compounds possessing 2° amino groups (e.g., **5ea** and **13**). Quite remarkably, the strategy also allowed us to introduce a peroxy group at C2 using TBHP (**17**), with no trace of oxidation of sulfur moiety in the resulting product. Importantly, access to such α-heteroatom-substituted peroxy compounds is highly important in both synthetic methodologies and biological contexts.[12] We next used thiol, which added at C2 in similar fashion to give **18** in 80% yield. Reaction with TBAF afforded the hydrolyzed ring-opened product **19**.

To demonstrate the utility of the synthesized compounds, we performed the deprotection of the benzyloxy group on a representative compound **3aa** using $Mo(CO)_6$, which led to compound **20** (85%) with a free NH group via selective N−O bond cleavage (Scheme 6). *N*-Alkylation of **20** with 1,4-dibromobutane delivered **21**, which could serve as a potential intermediate for the preparation of analogues of a known antipsychotic agent.[8c]

Scheme 6. Further Studies



In summary, we have developed a new approach for efficient synthesis of highly functionalized thiazolidin-4-ones utilizing an azaoxyallyl cation intermediate and thiocarbonyls. This is another rare example of reactive thiocarbonyls participating in the [3 + 2] annulation as a two-atom unit. Furthermore, the C2 amino group in the 2-aminothiazolidin-4-ones displayed a high degree of lability in HFIP, which opened up the opportunity to use it as the latent reactive group for late-stage modifications and enabled the introduction of a very wide range of functional groups at the C2 position. Importantly, this chemistry worked efficiently without the need of any Lewis acids or metal catalysts. For the current [3 + 2] annulation, the prerequisite *N*-benzyloxy group was cleaved easily to free the NH group, which was amenable to subsequent functionalizations. More details of the mechanistic studies on S_N1-type solvolysis of 2-aminothiazolidin-4-ones possessing the tertiary amino group in HFIP medium and further applications are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01933.

Experimental procedures and characterization data for all compounds and crystal data for **3am** and **5am** (PDF)

Accession Codes

CCDC 1918619−1918620 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.S. thanks SERB, New Delhi, for funding (ECR/2016/001474). V.J. and B.M. thank UGC and CSIR, New Delhi, for fellowships. K.S. thanks SERB, DST (PDF/2017/000097). J.S. thanks the Director of CBMR for research facilities. D.D. thanks DST-FIST for X-ray facility at SPS, JNU.

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DOI: 10.1021/acs.orglett.9b01933
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DOI: 10.1021/acs.orglett.9b01933
Org. Lett. XXXX, XXX, XXX−XXX