arxada

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Custom Development & Manufacturing Organization (CDMO)

From Lab to Production: When Triketene is bridging the gap towards Cyclobutane derivatives

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Despite growing interest, cyclobutane-containing small molecules remain scarce on the market. While many vendors have hundreds of g-scale cyclobutane building blocks available and knowing that Arxada, as a multi-mt manufacturer can access and incorporate this moiety, we realized that the gap in the kg-scale scale required during the development phase, could be worth bridging. Accessing these intermediate quantities is now doable thanks to Arxada's integrated ketene/diketene network.

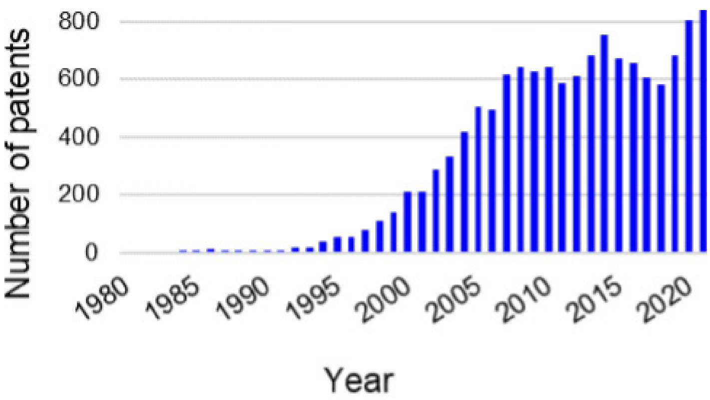
From Lab to Production: When Triketene is bridging the gap towards Cyclobutane derivatives

At lab scale (grams), several cyclobutane building blocks are available. At commercial scale (tons), manufacturers such as Arxada know how to prepare and incorporate this moiety. However, in the middle scale range (kilograms), it can be difficult to access cyclobutane building blocks that will allow for rapid and versatile diversification once a lead is identified. For this reason, the cyclobutane-containing hits are sometimes seen as difficult to pursue, and dropped. In order to bridge this gap and allow such derivatives to be further explored, Arxada took advantage of its ketene/diketene integrated network and prepared a stable cyclobutane derivative, the dicyclohexylammonium 3-oxocyclobut-1-en-1-olate, from its unstable precursor, the triketene.

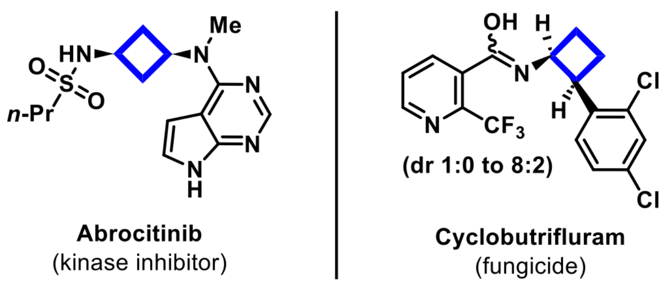
Small-strain carbocycles are highly sought after moieties due to their sp³-rich characteristics and potential for bioisosteric switches, not to mention subsequent IP opportunities.[1] The cyclobutane is a very particular member of this group, and a growing interest in the corresponding derivatives can be seen by the increasing number of patents on the topic, as well as some recent developments (Figure 1).

Figure 1: Cyclobutane-containing derivatives: a popular motif with raising interest

1.a. Patents filled involving cyclobutane-containing active ingredients for therapeutics or agricultural uses over the last 40 years[2]



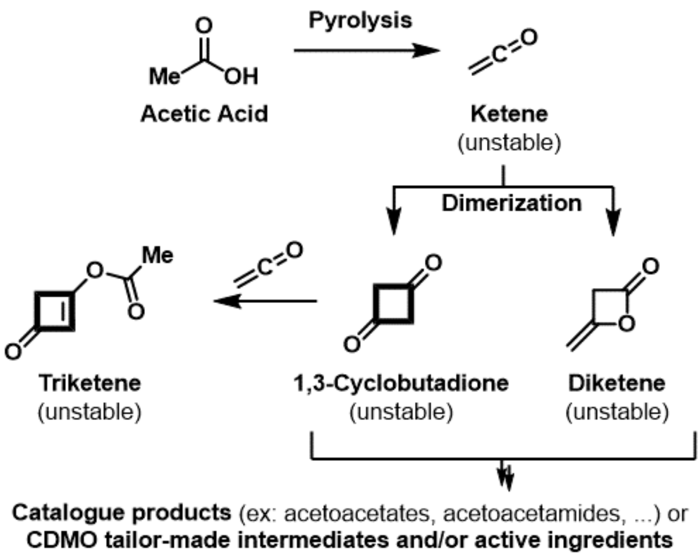
1.b. Example of two recently approved or in development active ingredients bearing a cyclobutane moiety



Nonetheless, if cyclopropyl, cyclopentyl, and cyclohexyl moieties are commonly seen, the presence of the corresponding 4-membered ring remains less frequent within the commercially available set of active ingredients. According to a recent article from AstraZeneca, this scarcity could result from the perception that these building blocks are challenging to source.[3] Indeed, the community seems to have no difficulty accessing numerous derivatives on small (mg to g) or large (ton) scales, but the intermediate scale (kg) needed during the development phase, seems challenging to secure.

At Arxada's production site in Visp (Switzerland), ketene and diketene are continuously produced from acetic acid, by pyrolysis (Figure 2). These highly reactive reactants/reagents, which are not transportable and have limited stability, are further derivatized on-site, leading to a variety of catalog products, or tailor-made intermediates.

Figure 2: Chemistries out of the acetic acid pyrolysis



The pyrolysis of acetic acid is producing ketene, which is quickly and predominantly dimerizing to form diketene. However, a small portion of ketene is following an alternative dimerization pathway, leading to 1,3-cyclobutadione. This dione is then instantly reacting with another equivalent of ketene, to form 3-acetoxy-2-cyclobuten-1-one, also called triketene. One can already see the cyclobutyl rings being formed during these transformations. Unfortunately, neither the 1,3-cyclobutadione nor the triketene is stable enough to be isolated and stored. If the described transformations do not allow for the isolation of a stable cyclobutane building-block, the Arxada CDMO branch can still harness these streams for further derivatization towards tailor-made intermediates and/or active ingredients.

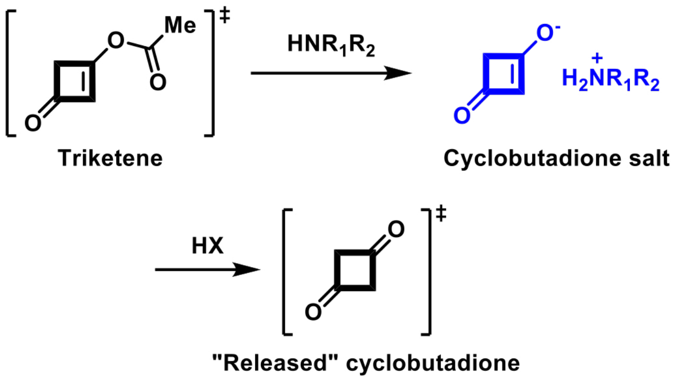
[1] D. J. Hamilton, M. Beemsterboer, C. M. Carter, J. Elsayed, R. E. M. Huiberts, H. F. Klein, P. O'Brien, I. J. P. de Esch, M. Wijtmans, *ChemMedChem* **2022**, *17*, e202200210.

[2] Search perfomed with SciFinder, in February 2022, restricted to: patent in "English", MW ≥ 250 g.mol⁻¹.

[3] M. R. Bauer, P. Di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storera, B. C. Whitehurst, *RSC Med. Chem.* **2021**, *12*, 448-471.

With the aim of making the 4-membered rings available to the market, including at the “middle scale” (kg) previously mentioned, the team designed a process allowing for triketene to be trapped, hence delivering a bench-stable cyclobutane building block (Figure 3).

Figure 3: Trapping triketene towards the corresponding stable dione salt, and subsequent release

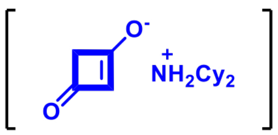


The reaction of triketene with certain amines allows for the isolation of the corresponding cyclobutadione salts with good to high yields and purities. These salts tend to exhibit high stabilities and can be shipped, or used as a reactant at a later time. Additionally, their acidification is allowing for 1,3-cyclobutadione to be released in the media.

Based on this chemistry, the stable dicyclohexylammonium 3-oxocyclobut-1-en-1-olate (CAS 137131-29-4) was fully characterized and synthesized at Arxada for its customers (Table 1).

Table 1. Product fact sheet: dicyclohexylammonium 3-oxocyclobut-1-en-1-olate

Structure



Product Information	
CAS Number	137131-29-4
Name	Dicyclohexylammonium 3-oxocyclobut-1-en-1-olate
Alternative names	Cyclobutadione salt Dione salt
Molecular formula	$C_{16}H_{27}NO_2$
Molecular weight	265.4 g.mol^{-1}
Form	Solid
Melting point	179°C
Color	Yellow to brown
Purity	≥ 98%

The dione salt can be prepared at a variety of scales, including the kilogram range where it can serve as a “source of cyclobutane” before further derivatization. For larger quantities and/or once a project reaches commercial volumes, Arxada can supply multiple metric tons of the desired dicyclohexylammonium 3-oxocyclobut-1-en-1-olate. Alternatively, Arxada will consider the development of these cyclobutane-containing intermediates and/or active ingredients directly from its ketene/diketene network.

In conclusion, a stable cyclobutadione building block was prepared directly from acetic acid, hence leveraging the supply chain headaches at development phases for such strained carbocycle. As a result, our collaborators can focus on what matters to them, whether it is finding tomorrow’s cures or supporting the food chain of soon to be 10 billion people.

Acknowledgments

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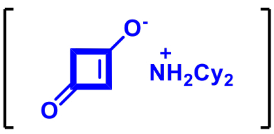
Our offer



- **A cyclobutane building block from kg to mt scale**
- **A stable salt available for rapid and versatile derivatization**
- **No more supply gap at the different phases of development**
- **More opportunities for backward integration of the resulting ingredients at larger scale**
- ***Focus on what matter to you***

For further information and/or if you would like Arxada to support your project(s), get in touch with:
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