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Custom Development & Manufacturing Organization (CDMO)

Quick Access to Ubiquitous Moieties: Diketene as a Versatile Door Opener for Acetoacetates and Further 1,3-substitution Patterns

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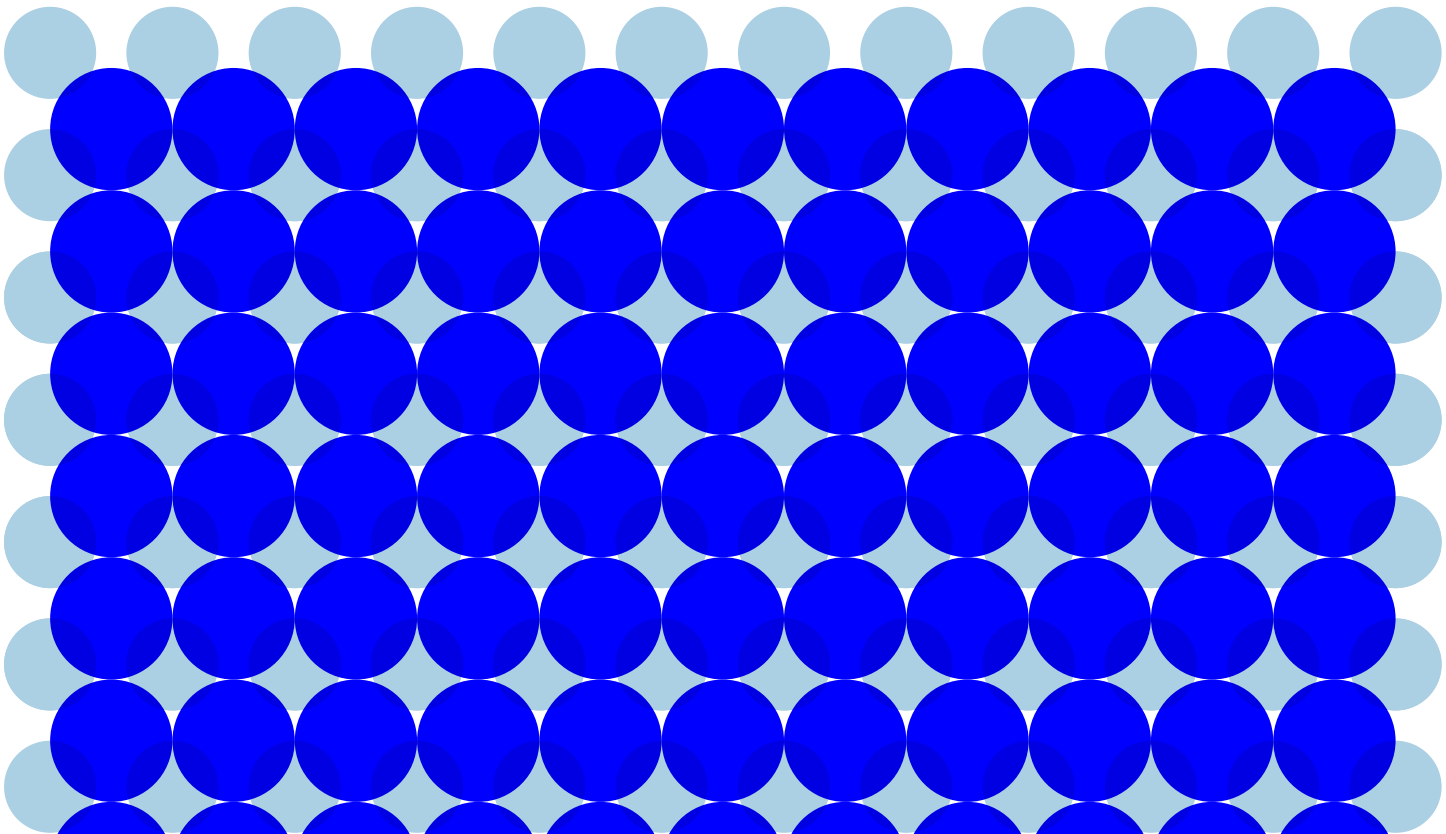
When buying what looks like a “simple reagent” such as methyl acetoacetate, who never asked her/himself what is the reagent’s reagent, or how great would it be to have the corresponding reagent with a methylpropyl, cyclopentane, or similar groups (instead of the methyl). By working with ketene/diketene, the reagent of the reagent, and indeed producing it, access to virtually all alternatives is possible.

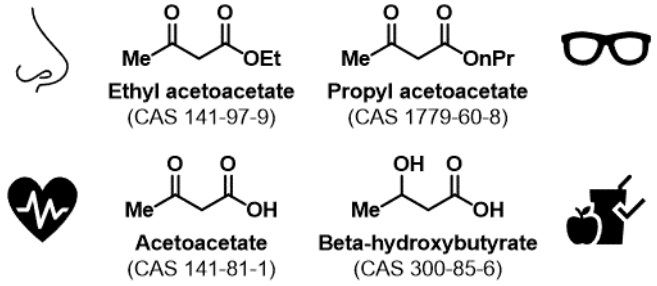


Quick Access to Ubiquitous Moieties: Diketene as a Versatile Door Opener for Acetoacetates and Further 1,3-substitution Patterns

Acetoacetates have a long successful history and can be seen as "basic" moieties for further derivatization into various 1,3-subsituted analogues.[1] Like all "basic" skeletons, it is therefore very important to develop fast and efficient transformations to obtain them. Diketene, itself coming from acetic acid, appears to be a great and versatile source of acetoacetates, with almost infinite options in terms of substitution pattern. Arxada is one of the established players in ketene/diketene production and chemistries, therefore also making itself unavoidable in the acetoacetates world.

Acetoacetates are commonly used reagents leading to numerous important building blocks or closely related products. Some simple examples are Ethyl acetoacetate, which is used by the flavor and fragrance industry due to its ethereal, fruity-apple, sweet, rum-like odor; Acetoacetate & Beta-hydroxybutyrate, naturally occurring in our body and sometimes used by the food industry; and Propyl acetoacetate, which is used as an anti-reflective coating agent (Figure 1).

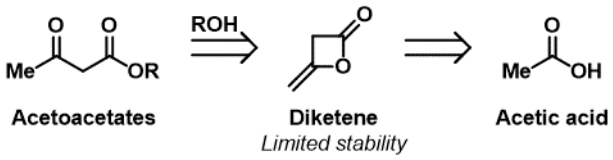
Figure 1. Selected examples of commercially relevant acetoacetate-derived products.



Other 1,3-substitution patterns commonly accessible from acetoacetates are malonates, crotonates, or beta-amino ester just to name a few. Thanks to the versatility of the chemical functions present in all these derivatives, someone skilled in the art would quickly realize the endless opportunities afforded by these moieties. One can also see many opportunities to further substitute the C-2 position.

Due to the broad use of the discussed derivatives, in order to unlock their potential, our community must rely on quick and efficient syntheses allowing to produce these. One very elegant production route involves diketene and appears to be a perfect opportunity, being versatile, highly atom-efficient, and sustainable (Scheme 1).

Scheme 1. Acetoacetates retrosynthetic analysis.

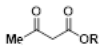
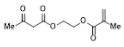
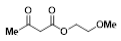
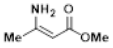
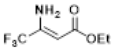
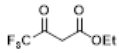
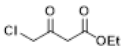
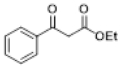


The desired acetoacetates can be prepared from the opening of diketene with an alcohol. Diketene can be obtained from the dimerization of ketene (not shown in the scheme), itself being produced from the pyrolysis of acetic acid. Whilst this process is highly selective with almost no waste, the limited stability of ketene/diketene is important to note (indeed this intermediate cannot be shipped or bought as such). Therefore, the acetoacetates, when based on diketene, must come from a producer equipped to operate the pyrolysis of acetic acid and subsequent opening on the same site.

Fortunately, Arxada happened to be producing its own ketene/diketene on its Visp site, and has a long-standing expertise in the manufacturing of diketene and the following transformations, both in dedicated and multipurpose plants. Taking advantage of its backward integration, Arxada nowadays has a broad portfolio of acetoacetates available at multi tons scale (Table 1).

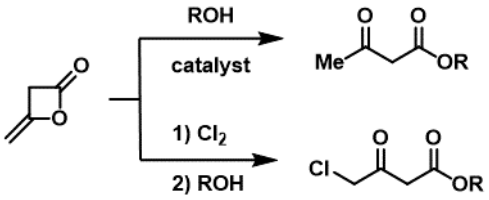
[1] By basic, we mean reagents/reactants involve early in the synthesis and/or with low complexity (and usually also a low molecular weight).

Table 1. Arxada portfolio of acetoacetates and related products.

Name	CAS-No	Abbreviation	Structure
Alkyl acetoacetates	105-45-3 141-97-9 542-08-5 1694-31-1	R=methyl: AAMe R=ethyl: AAEt R=isopropyl: AAIP R=*t*-butyl: AA-*t*-butyl	
Acetoacetoxyethyl methacrylate	21282-97-3	AAEMA	
2-Methoxyethyl acetoacetate	22502-03-0	AAmethoxyethyl	
Methyl 3-aminocrotonate	14205-39-1	ACMe	
Ethyl 3-amino-4,4,4-trifluorocrotonate	372-29-2	ACEt,Trifluor	
Ethyl 4,4,4-trifluoro-acetoacetate	372-31-6	AAEt,TF	
Ethyl 4-chloroacetoacetate	638-07-3	CAAEt	
Ethyl benzoylacetate	94-02-0	BESethyl	

Whilst acetoacetates can easily be obtained from diketene and an alcohol, the corresponding chloro-derivatives (such as CAAEt) require an additional step involving chlorine (Scheme 2).

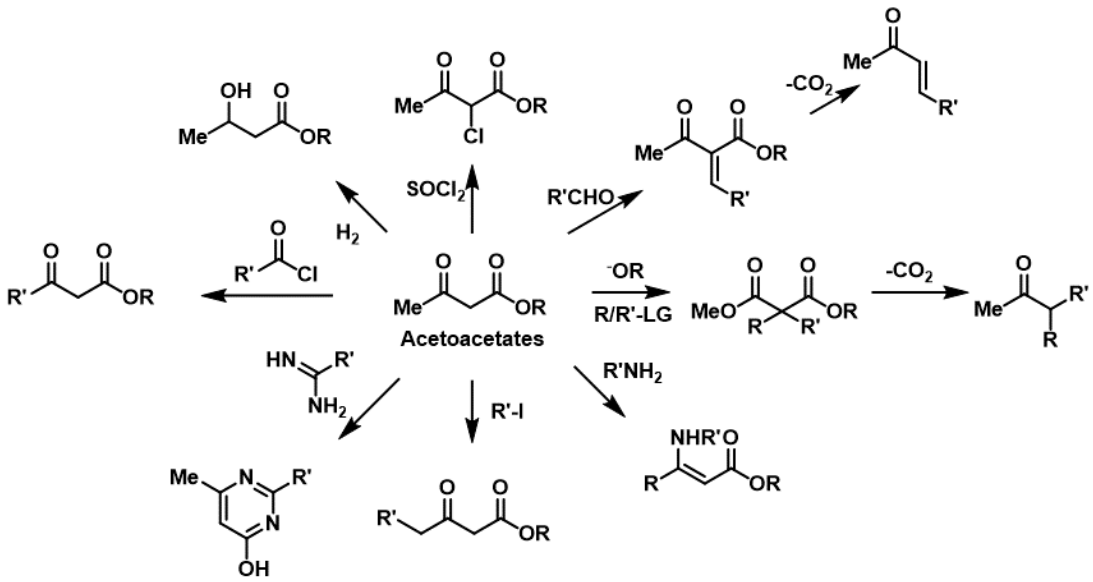
Scheme 2. Synthesis of acetoacetates and corresponding chloro-derivatives from diketene.



In addition, the corresponding trifluoro (ie $CF_3C(O)$ instead of $ClCH_2C(O)$ or $MeC(O)$) can also be obtained from a similar pathway.[2]

Most of the products presented up to this part are actual pieces from the Arxada portfolio, which can be found online.[3] However and as already mentioned, the presented chemistry (ie the diketene opening) could virtually work with "all" alcohols, then virtually leading to "any" acetoacetates. For those in need of a specific derivative that is not part of the public portfolio, Arxada's custom and development manufacturing team could develop a process tailored to specific needs.[2] In addition, all presented products are great building blocks for further derivatization, making the use of acetoacetates almost limitless (Scheme 3).

Scheme 3. Selected examples of transformations from acetoacetates.



[2] For more information, please contact the team (myproject@arxada.com).

[3] Portfolio available at: https://www.arxada.com/en/products?sortType=Ascending.

Here again, virtually all derivatizations could be prepared in Visp within Arxada's multipurpose assets.

In conclusion, diketene is offering a versatile, low waste, and efficient access to acetoacetates and other 1,3-derivatives. As this key reagent is prepared directly on-site, Arxada positions itself as an important player in the acetoacetates market, and thanks to its backward integration, can strengthen the supply chain of its key customers.

Acknowledgments

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Our offer

- **Backward integration for acetoacetates and other 1,3-derivatives**
- **Only ketene/diketene manufacturer in Europe**
- **Long experience in ketene/diketene chemistries**
- **Ability to derivatize on-demand**
- ***Focus on what matters to you***

If you would like to further discuss Arxada's portfolio, get in touch with: **performance.intermediates@arxada.com**, and for more information on bespoke projects, get in touch with: **myproject@arxada.com**

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