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Simple and Efficient Industrial Preparation of Various Trifluoromethyl Ketones and Derivatives

Dominique Michel*

Abstract: Trifluoromethyl ketones are important tools in organic synthesis, useful especially for the production of complex fluorinated compounds. The preparation of ethyl 4,4,4-trifluoroacetoacetate and several attractive applications are described, as well as a new route leading to different fluorinated pyruvaldehydes and some examples of applications.

Keywords: Building blocks · Ethyl 4,4,4-trifluoroacetoacetate · Fluorinated pyruvaldehydes · Trifluoromethyl ketones

The introduction of fluorine into organic molecules as a way to modify their chemical properties has been extensively exploited in various fields of agrochemical, pharmaceutical and polymer chemistry. This has resulted in an increasing number of new fluorinated compounds. The elaboration of new synthetic methods to introduce fluorinated substituents remains therefore a great challenge for the synthetic chemist [1–6].

Among the numerous and various fluorinated compounds, ketones incorporating fluorine substituents are of special interest, not only for their roles as synthons for the preparation of more complex molecules, but also for their own biological properties as enzyme inhibitors for example [6]. LONZA, being a major custom manufacturer for the life science industry, produces several fluorinated key intermediates and some attractive examples will be presented in this article.

The first example is ethyl 4,4,4-trifluoroacetoacetate (**1**). This versatile building block, which can be used for the preparation of many derivatives like pyrimidines, quinolines or pyrazoles *(vide infra)*, is produced on multi-ton scale at LONZA by insertion reaction of trifluoroacetyl chloride with ketene (**2**), the latter being produced in a dedicated plant starting from acetic acid (**3**). This reaction leads in a first step to the acyl chloride **4**, which is immediately quenched with ethanol affording the desired building block **1** (Scheme 1). LONZA is one of the world's leading manufacturers of ketene, thus guaranteeing an optimal backwards integration of this process.

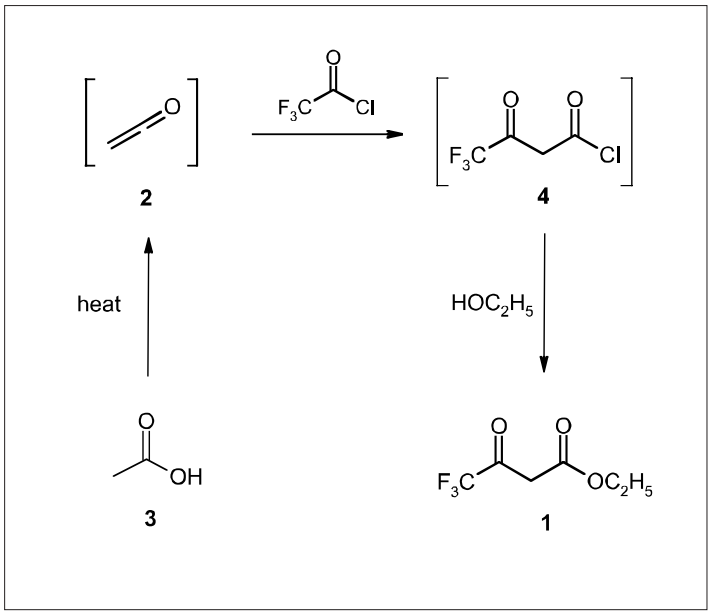
Ethyl 4,4,4-trifluoroacetoacetate (**1**) can be used for the preparation of other building blocks such as the pyrimidines **5–7** by reaction with acridine, guanidine or *in-situ* generated O-isopropylisourea, respectively. The reactions are performed in alcohols at 60–120 °C and the desired products are isolated in 49–85% yield (Scheme 2) [7–9].

All these pyrimidines can be further used as building blocks for the preparation of more complex pyrimidines or purines [7–11]. For example, **7** can be used for the preparation of fluacrypyrim (**8**) in one step, by coupling reaction with the benzyl bromide **9** under basic conditions (Scheme 3) [10][11]. Fluacrypyrim (**8**) is a new insecticide recently launched by Nippon-Soda and sold under the trade name of Titaron.

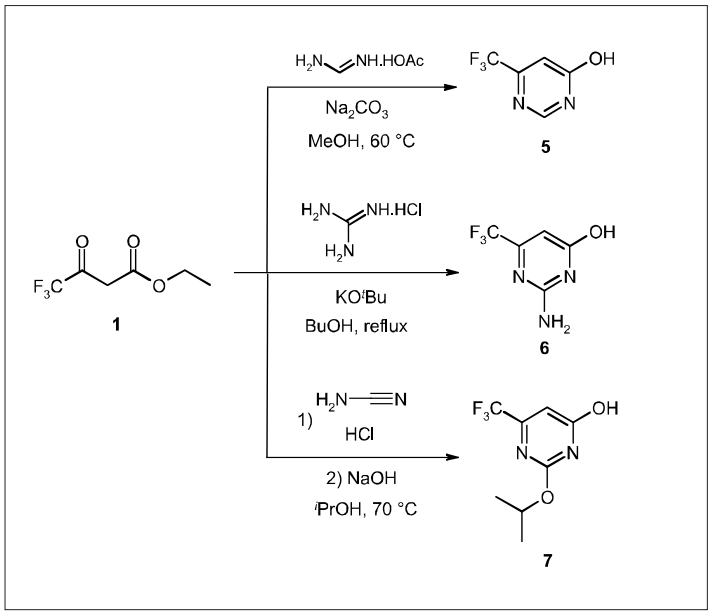
The fluorinated ester **1** can also be used for the preparation of the well-known antimalaria drug mefloquine (**10**) invented by Hoffmann La Roche, better known to travellers under its trade name of Lariam [12]. In a first step, **1** is treated with 2-trifluoromethylaniline (**11**), then brominated with phosphorous tribromide affording the bromoquinoline **12** in 75% overall yield. Further treatment of **12** with butyllithium and subsequent quenching of the *in-situ* generated lithioquinoline with 2-pyridaldehyde (**13**) lead then to the pyridine **14**. Finally, **14** is subjected to a catalytic hydrogenation in the presence of platinum as catalyst affording the desired product **10**. The overall yield of the two last steps is 70% (Scheme 4) [12].

(*R*)-Ethyl 4,4,4-trifluoro-3-hydroxy-butanoate (**15**) is an important building block for the preparation of several pharmaceuticals. It can be prepared from ethyl 4,4,4-trifluoroacetoacetate (**1**) either by reduction followed by a lipase-promoted enzymatic resolution [13], by enzymatic reduction [14][15], or by asymmetric hydrogenation [16][17]. As none of the known methods are really easy to perform and are not efficient enough to be used on industrial scale in our opinion, we decided to investigate this reduction thoroughly, and we found that the substrate can be efficiently reduced enzymatically when whole cells of *Escherichia coli* containing two plasmids are used. One plasmid carries an aldehyde reductase gene from the yeast *Sporobolomyces salmonicolor* and catalyses the reduction. The second plasmid carries a glucose dehydrogenase gene from *Bacillus megaterium* and generates NADPH from $NADP^+$. The enzymatic reduction is performed in a two-phase system to avoid the inhibition of the

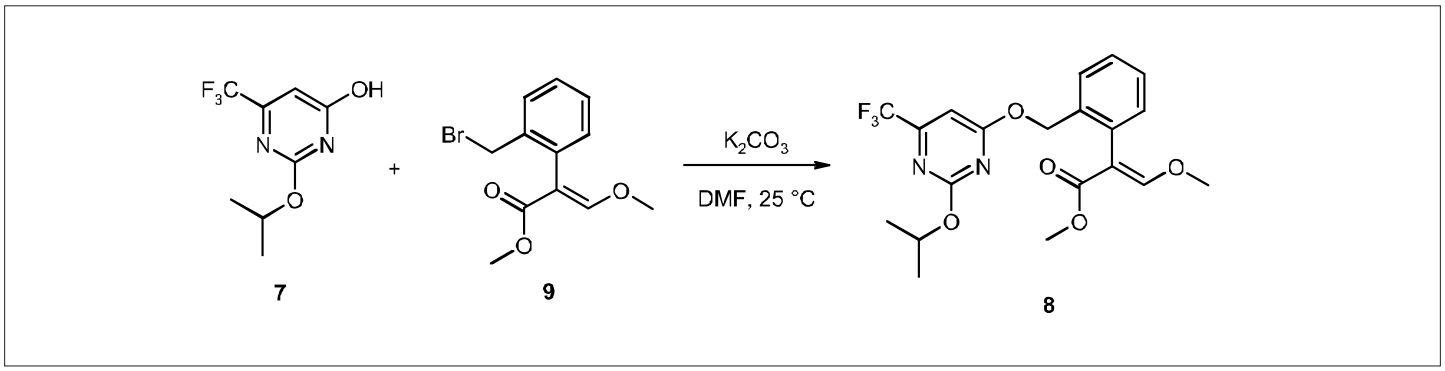
*Correspondence: D. Michel
LONZA Ltd
Valais Works
CH-3930 Visp
Tel.: +41 27 948-5807
Fax: +41 27 947-5807
E-Mail: dominique.michel@lonza.com
http://www.lonza.com



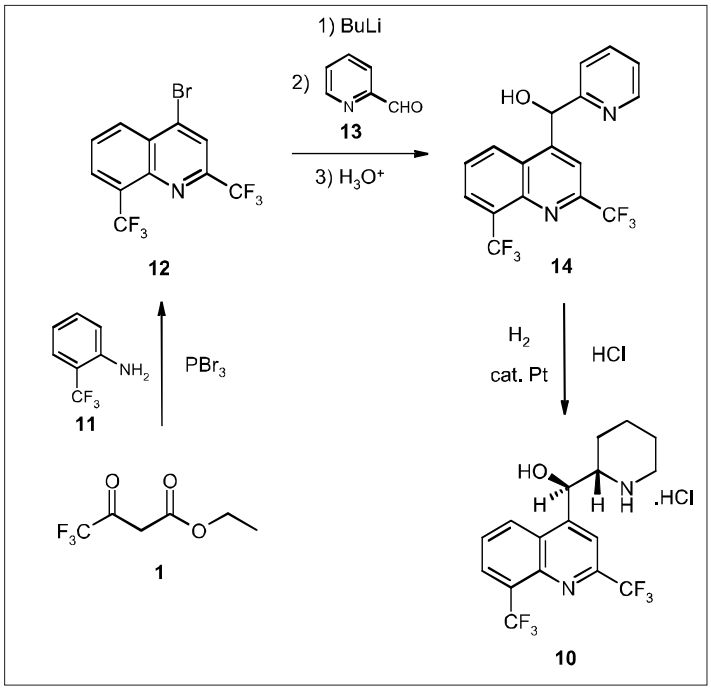
Scheme 1. The LONZA industrial process leading to ethyl 4,4,4-trifluoroacetoacetate (**1**)



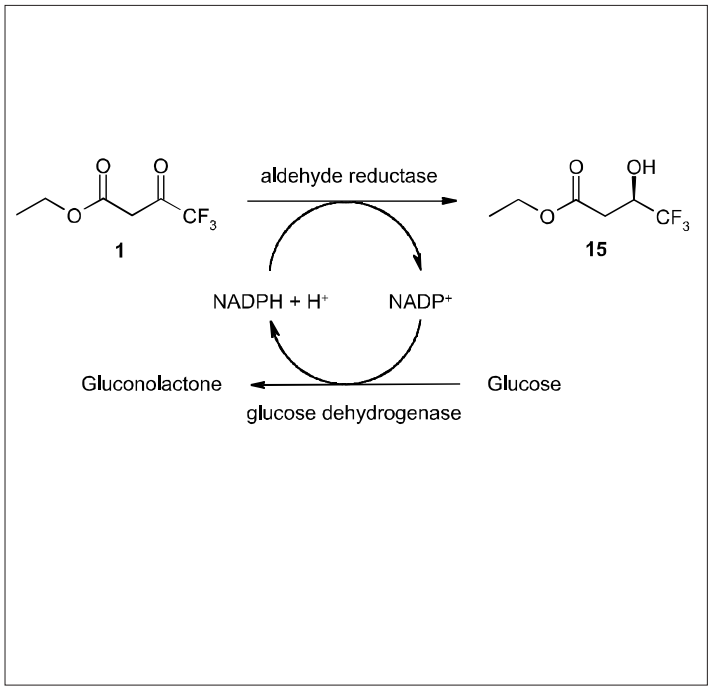
Scheme 2. Preparation of some pyrimidine derivatives at LONZA which are based on ethyl 4,4,4-trifluoroacetoacetate (**1**)



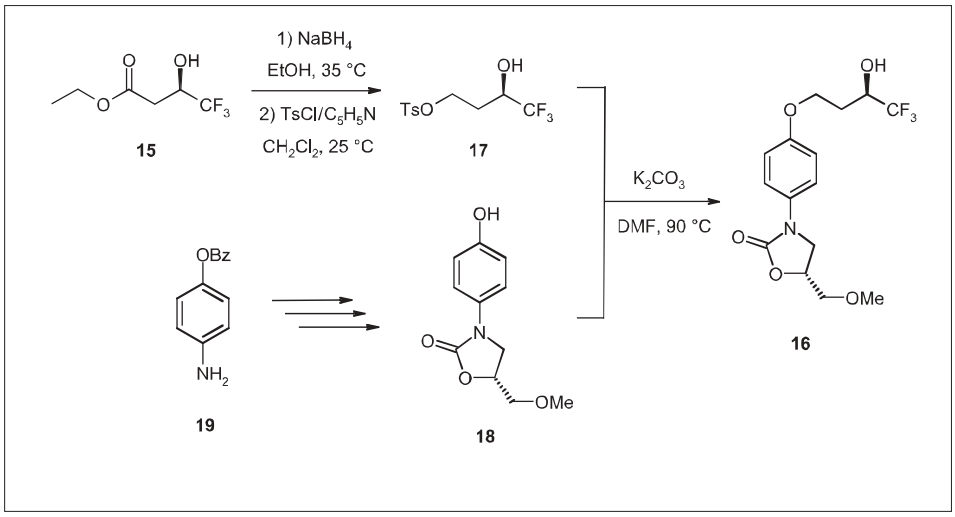
Scheme 3. Synthesis of fluacrypyrim (**8**): final step



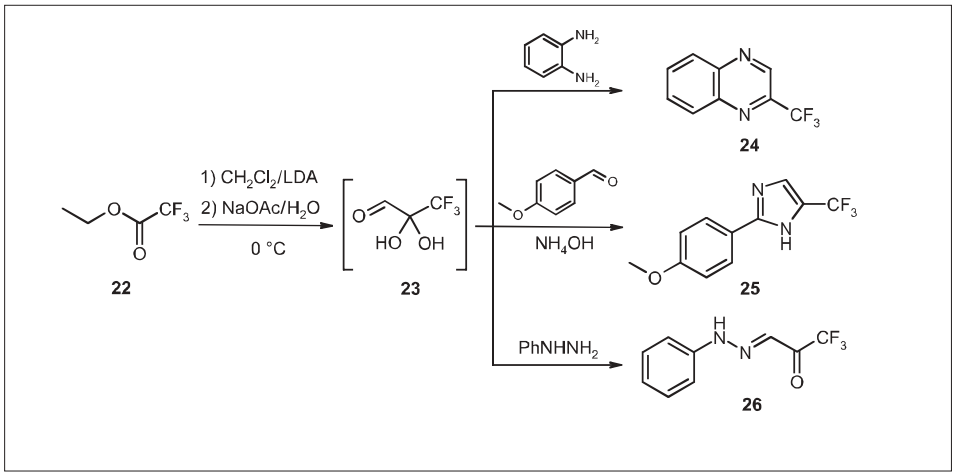
Scheme 4. The original route leading to the mefloquine (**10**)



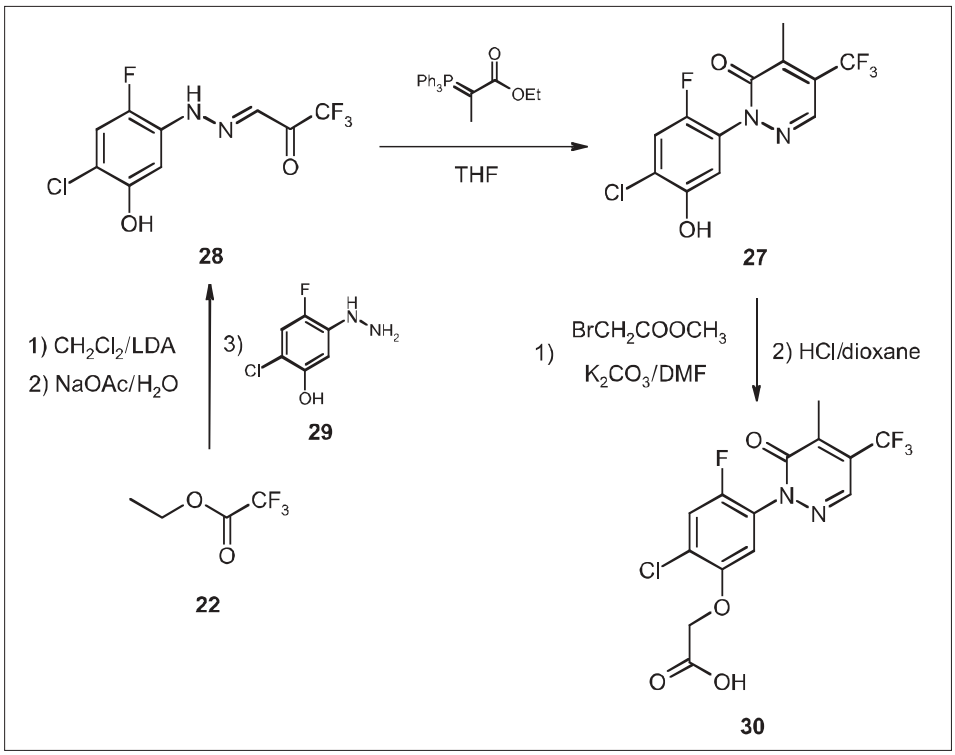
Scheme 5. The stereoselective reduction of **1** by an aldehyde reductase from *Sporobolomyces salmonicolor* in *Escherischia coli*



Scheme 6. Preparation of benfloxatone (**16**) according to the Synthelabo process



Scheme 7. Trifluoropyruvaldehyde hydrate (**23**); preparation and examples of use



Scheme 8. The synthesis of the Flufenpyr (**30**)

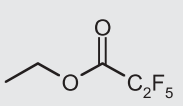
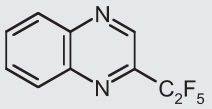
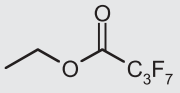
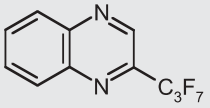
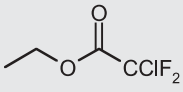
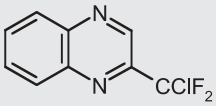
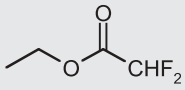
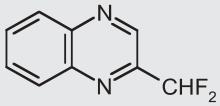
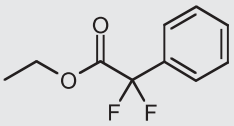
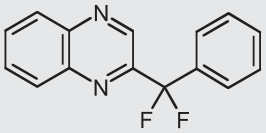
reductase by the substrate and product. With this process, the alcohol **15** can be readily obtained on large quantities in 50% yield and with ee values of more than 99% (Scheme 5) [18].

The alcohol **15** can further be used for the preparation of befloxatone (**16**), an antidepressant monoamine oxidase-A inhibitor developed and commercialized by Synthelabo [19]. Thus, **15** is initially converted into the tosylate **17** in 54% yield by sodium borhydride reduction and tosylation, respectively. In the second step, **17** is coupled with the optically active oxazolidinone **18** using potassium carbonate as base and befloxatone (**16**) is obtained in 61% yield. The building block **18** can be prepared in three steps from 4-benzyloxyaniline (**19**) (Scheme 6) [19].

We furthermore were strongly interested in the preparation of fluorinated pyruvaldehydes as building blocks for the construction of fluorinated heterocycles like quinoxalines or imidazoles, or also for the preparation of fluorinated phenylhydrazones *(vide infra)*. According to our knowledge, only two fluorinated pyruvaldehydes were already known from the literature: fluoropyruvaldehyde (**20**) and trifluoropyruvaldehyde (**21**). The former can be obtained in five steps starting from fluoroacetic acid [20]. The second one is obtained in a simpler way from either 3,3-dibromo-1,1,1-trifluoroacetone, or from 3,3-dichloro-1,1,1-trifluoroacetone, upon treatment with aqueous sodium acetate [21]. These ketones can furthermore be obtained by bromination of trifluoroacetone [22], or by reaction of pentachloroacetone with hydrogen fluoride [23]. However, those routes leading to the desired compounds are relatively long and tedious. In addition, corrosive and toxic reagents like hydrogen fluoride are used.

Therefore, our objective was to develop a new route that can be extended to other fluorinated pyruvaldehydes and which should be easy to perform and should require cheap starting material. Our idea was simply to add dichloromethyllithium to a fluorinated ester like ethyl trifluoroacetate (**22**) as described for many other non-fluorinated esters [24]. Thus, the metalation of methylene chloride with lithium dicyclohexylamide or lithium diisopropylamide (LDA) followed by quenching with ethyl trifluoroacetate and an aqueous solution of sodium acetate, respectively, was performed and effectively yielded an aqueous solution of trifluoropyruvaldehyde (**21**), existing principally as the hydrate **23** [21]. In a first run of experiments, the metalation reaction was carried at –78 °C as reported in the original literature [24], however, in a second run, we found that the reaction can be performed at 0 °C as well (Scheme 7) [25]. Although LONZA can perform reac-

Table. Preparation of various fluorinated pyruvaldehydes and derivatives.

Entry	Fluorinated Ester	Corresponding Quinoxaline	Yield
1	 **31**	 **36**	36%
2	 **32**	 **37**	18%
3	 **33**	 **38**	87%
4	 **34**	 **39**	82%
5	 **35**	 **40**	54%

tions at –80 °C on large scale, we prefer to use higher temperature if possible as those conditions often result in a better economy of the process.

The obtained fluorinated hydrate **23** solution was further treated with 1,2-phenylenediamine affording the quinoxaline **24** in 80% overall yield [25]. The imidazole **25** and the phenylhydrazone **26** could be also be prepared using either anisaldehyde or phenylhydrazine instead of 1,2-phenylenediamine in 65% and 77% overall yield, respectively (Scheme 7) [25].

Also, pyridazine-3-ones can readily be obtained from hydrazones by reaction with stable phosphorus ylids [26]. For example, 2-(4-chloro-2-fluoro-5-hydroxyphenyl)-4-methyl-5-trifluoromethylpyridazine-3-one (**27**) was prepared in 58% yield from the hydrazone **28**, which was itself obtained by reaction of the phenol **29** with the hydrate **23** (in 49% yield, based on the ester **22**). The compound **27** is the advanced intermediate of Flufenpyr (**30**), a potent herbicide recently developed by Sumitomo (Scheme 8) [26].

The newly developed method was then extended to other fluorinated esters [27]. Surprisingly, with an ester bearing a longer perfluorinated chain, such as ethyl pentafluoropropionate (**31**) or ethyl heptafluorobutyrate (**32**), the yields of the corresponding quinoxalines **36** and **37** are much lower (36 and 18%, respectively, Table, entries 1 and 2). On the other hand, when ethyl chlorodifluoroacetate (**33**) and ethyl difluoroacetate (**34**) were used, the corresponding quinoxalines **38** and **39** were isolated in yields of 87 and 82%, respectively (Table, entries 3 and 4). Finally, we also tried to use the ethyl α,α-difluoro-α-phenylacetate (**35**) [28] and in that case, the corresponding quinoxaline **40** was obtained in 54% yield (Table, entry 5).

In this overview only a few examples could be summarized. The preparation of many other fluorinated ketones and derivatives using the described technologies may be required in the future in order to cover demands for new fluorine-containing active ingredients to be developed by the life science industry.

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