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One-pot synthesis of difluoromethyl ketones by a difluorination / fragmentation process

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Daniel J. Leng, Conor M. Black and Graham Pattison*

Difluoromethyl ketones are an under-studied class of ketones which have great potential as useful building blocks for materials and drug design. Here we report a simple and convenient synthesis of this class of compounds via a one-pot difluorination / fragmentation of 1-trifluoromethyl-1,3-diketones which should now allow the chemistry of difluoromethyl ketones to be fully developed.

Introduction

Fluorinated organic compounds have seen a recent surge in popularity due to the advantageous effects fluorine can impart on molecules in applications ranging from pharmaceuticals to materials.[1] In particular, the trifluoromethyl (CF_3) group has seen widespread application as a polar, lipophilic functional group which can modulate important molecular properties such as bioavailability and dipole moment.[2] As a result, a large number of methods for the introduction of trifluoromethyl functionality into organic molecules are becoming available.

The difluoromethyl (CF_2H) group is another fluorinated moiety of great interest as, like the CF_3 group it is lipophilic, yet unlike CF_3 groups, difluoromethyl functionality can also be engaged as a hydrogen bond donor.[3] However, the properties and applications of difluoromethyl (CF_2H) compounds are much less well-known than their trifluoromethyl analogues as there are few good, general methods available for their synthesis.[4] Methods include the deoxygenative fluorination of aldehydes with reagents such as the toxic and explosive DAST,[5] or modern, safer alternatives such as Deoxofluor or XtalFluor.[6] Other possibilities for the synthesis of difluoromethyl compounds include the use of Me_3SiCF_2H[7] and difluorocarbene precursors,[8,9] amongst other assorted reactions.[10]

In particular, difluoromethyl-substituted carbonyl compounds would be of great interest, both for specific medicinal and materials applications, as well as valuable synthetic intermediates. Trifluoromethyl ketones have proven to be valuable synthetic building-blocks,[11] yet the synthesis of their difluoromethyl ketone analogues is difficult. Current approaches for their production tend to be non-general, sometimes low-yielding and often require the use of sensitive organometallics. These include reports on imine and enamine difluorination,[12] Mg-mediated defluorination of CF_3-ketones,[13] additions of Grignards to ethyl difluoroacetate,[14] additions of Ag-CF_2H complexes to acid chlorides[15] and reactions of electron-rich arenes with difluorinated iminium salts.[16] This lack of efficient synthetic routes for the study of difluoromethyl ketones has led to their chemistry currently being underdeveloped.[17] Here, we report a new, convenient and efficient route for the synthesis of CF_2H ketones which should allow their chemistry to be studied in full.

The key difficulty in the synthesis of difluoromethyl ketones is that methyl ketones are not sufficiently activated to undergo difluorination and typically undergo mainly monofluorination, even in the presence of excess fluorinating reagents. The addition of a single fluorine atom may in fact reduce the acidity and nucleophilicity of a carbonyl α-carbon through lone pair repulsion of fluorine with an adjacent developing negative charge.

We were therefore drawn towards 1,3-dicarbonyl compounds as precursors for three reasons (Figure 1): (1) these should be more activated towards difluorination; (2) the additional carbonyl substituent should act as a blocking group,

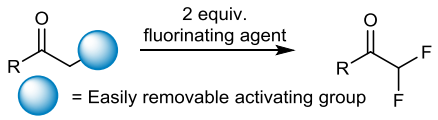


Figure 1: Synthetic design plan for syntheisis of difluoromethyl ketones

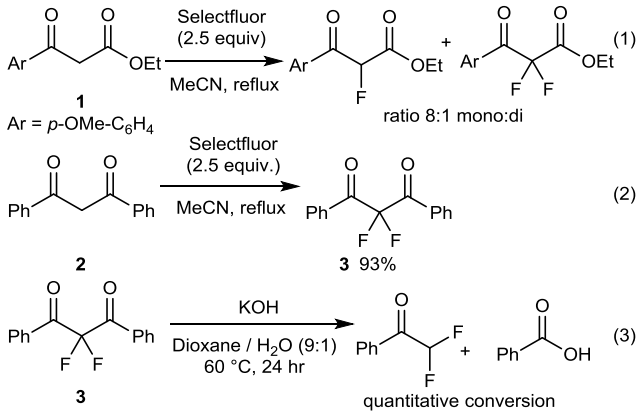
[a] Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry. CV4 7AL. Email: graham.pattison@warwick.ac.uk

Electronic Supplementary Information (ESI) available: Full experimental information, compound characterization and copies of NMR spectra See DOI: 10.1039/x0xx00000x

preventing trifluorination; (3) many 1,3-dicarbonyl derivatives are easily cleaved, which would reveal the desired CF_2H ketone.

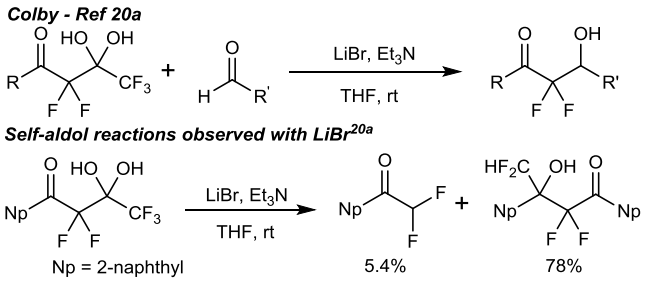
Results and Discussion

Our strategy therefore relied initially on the establishment of a robust protocol for difluorination of 1,3-dicarbonyl compounds.[18] Whilst β-ketoester **1** yielded a mixture of mono- and di-fluorinated material on fluorination with 2.5 equivalents of Selectfluor (eq. 1), 1,3-diketone derivatives were more successful and yielded the difluorinated product cleanly. For example, symmetrical diketone **2** readily underwent clean difluorination (eq. 2) and we were pleased to discover that difluorinated diketone **3** could be fragmented to the difluoromethyl ketone in the presence of KOH (eq. 3).[19]



However, we felt that the requirement for a symmetrical 1,3-diketone would lower the potential utility of this process. We therefore required a 1,3-diketone derivative that was both highly activated towards difluorination, easily synthesized and easily cleaved in a high-yielding and regioselective manner.

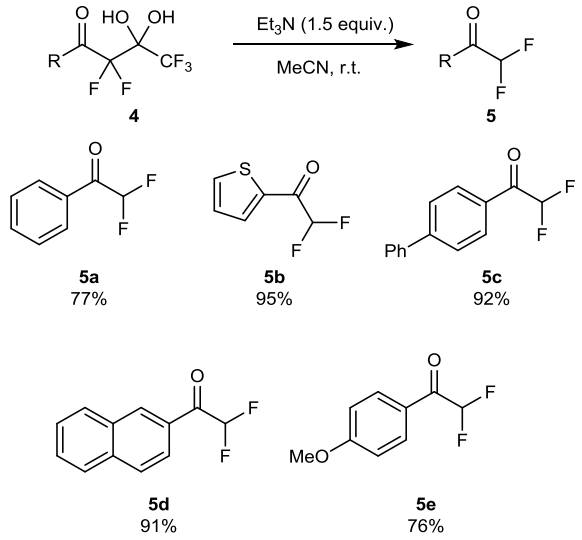
Electronic bias of a 1,3-diketone system may provide the necessary regioselectivity in the fragmentation step. We noted recent work on the cleavage and trapping with electrophiles of 1-trifluoromethyl-2,2-difluoro-1,3-diketones[20,21] in the presence of base and felt that 1-trifluoromethyl-1,3-diketones might be ideal substrates for the development of a difluorination / fragmentation process. The electron-withdrawing nature of the trifluoromethyl group means that 1-trifluoromethyl-1,3-diketones exist exclusively in the enol form and as such are highly activated towards difluorination. They also undergo cleavage in a highly regioselective fashion with the exclusive loss of trifluoroacetate which would allow a desired difluoromethyl ketone to be isolated. However, Colby has reported that the enolate formed in the presence of Et_3N and LiBr on cleavage of 1-trifluoromethyl-2,2-difluoro-1,3-diketones is highly reactive and undergoes self-aldol processes very rapidly, giving very poor yields of the difluoromethyl ketone (Scheme 1).[20a] Our aim was to establish conditions under which these self-aldol reactions could be prevented and allow the desired difluoromethyl ketone to be isolated.[22]



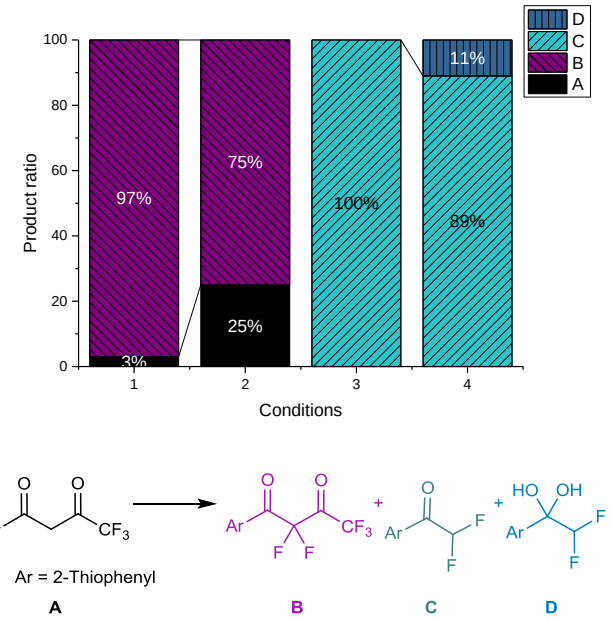
Scheme 1: Previous results by Colby *et. al.*

Our initial investigations therefore focused on 1-trifluoromethyl-2,2-difluoro-1,3-diketones as starting materials, which exist solely in the hydrate form due to the high electrophilicity of the highly fluorinated ketone group. We prepared a range of hydrated 1-trifluoromethyl-2,2-difluoro-1,3-diketones by Claisen condensation of various methyl ketones with ethyl trifluoroacetate, followed by difluorination with 2.5 equiv. of Selectfluor. We then sought to establish conditions for the fragmentation process which maximized the yield of difluoromethyl ketone, whilst suppressing any self-aldol processes. Critically, we found that the absence of LiBr from the reaction was key to suppressing the formation of competing self-aldol products. Several bases could be used to promote the fragmentation; we found 1.5 equiv. of Et_3N to be optimal in terms of product yield and purity. Alkali metal hydroxides tended to give varying amounts of the self-aldol product.[23] We then demonstrated that these conditions were suitable for the fragmentation of a range of 1,1,1,3,3-pentafluoro-2,4-diketones (Scheme 2).

We then aimed to improve the convenience of this process and to develop a one-pot difluorination-fragmentation reaction which would provide an effective route to difluoromethyl compounds. The addition of water is key to the success of this one-pot protocol. Under anhydrous conditions, fragmentation was greatly slowed, leading to a difluorinated dicarbonyl compound **B** being observed as the major product



Scheme 2: Fragmentation of 1,1,1,3,3-pentafluoro-2,4-diketones



Conditions 1: 2.5 equiv. Selectfluor, 1.5 equiv. Et_3N, reflux
Conditions 2: 2.5 equiv. Selectfluor, 3 equiv. Et_3N, reflux
Conditions 3: 2.5 equiv. Selectfluor, reflux, 2h
THEN H_2O (2 equiv.), Et_3N (5 equiv.), r.t., 16h
Conditions 4: 2.5 equiv. Selectfluor, reflux, 2h
THEN H_2O (100 equiv.), Et_3N (5 equiv.), r.t., 16h

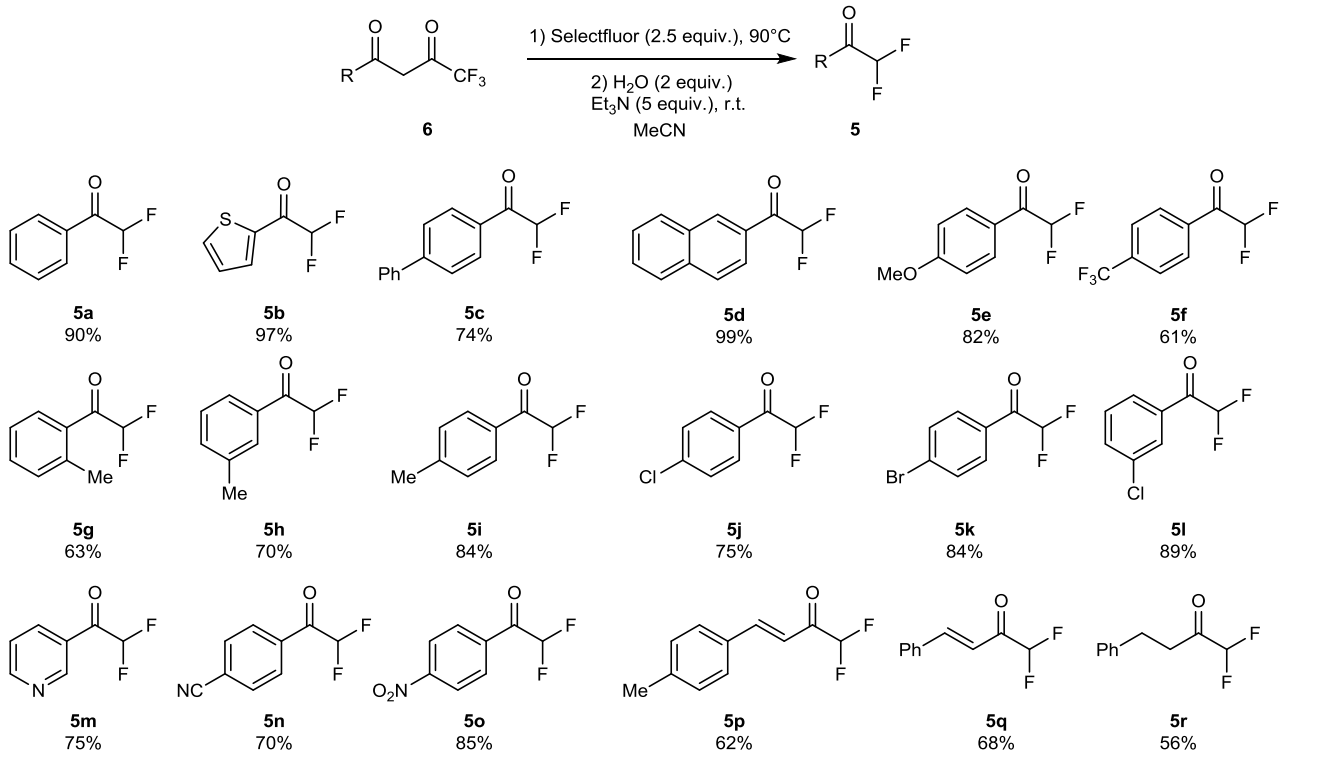
Figure 2: Product distribution in optimizing one-pot process

(Figure 2, conditions 1, 2). Instead, if difluorination is first performed under anhydrous conditions, followed by the addition of water and triethylamine to promote the fragmentation, the difluoromethyl ketone **C** is formed selectively (conditions 3). This suggests the importance of hydrate formation for fragmentation, and it is likely that deprotonation of the hydrate leads to a retro-Claisen-like process, release of trifluoroacetate and formation of the difluoromethyl ketone. Yet the amount of water added should be carefully controlled to 1-2 equivalents. In the presence of a large excess of water (~ 100 equiv.) the difluoromethyl ketone products themselves were also susceptible to hydrate **D** formation and decomposition processes which led to a decrease in isolated yield of the difluoromethyl ketone (Conditions 4).

After some brief optimization, the following conditions were established. In acetonitrile, 1-trifluoromethyl-1,3-diketones were first β-difluorinated using 2.5 equivalents of Selectfluor at reflux, followed by the addition of water and triethylamine to the cooled reaction mixture. This led to fragmentation, yielding the difluoromethyl ketone under very mild conditions.

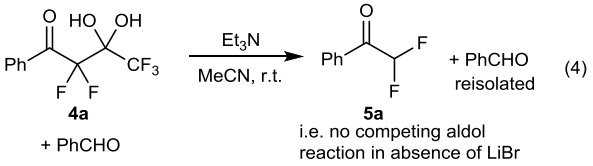
A range of electron-rich and electron-poor aromatic, heterocyclic, alkenyl and alkyl difluoromethyl ketones could be prepared by this difluorination/fragmentation approach, in generally very good yields (Scheme 3). Some of the difluoromethyl ketone products do have appreciable volatility and solvent should be removed from samples with care to prevent losses. Derivative **5a** was additionally prepared on a 5 mmol scale in 69% yield, demonstrating the utility of this process for the preparation of difluoromethyl ketone building-blocks.

The role of lithium salts in these fragmentation processes is



Scheme 3: One-pot difluorination / fragmentation for the synthesis of difluoromethyl ketones

of great interest. Our conditions are very similar to those reported by Colby, except for the absence of LiBr in this work.[20a] This had a striking effect on reaction outcome. In the absence of LiBr the fragmentation and loss of trifluoroacetate is significantly slowed (reactions were complete in 3 minutes in the presence of LiBr), yet the tendency to undergo competing aldol processes is reduced. Colby reported that in the presence of LiBr yields of difluoromethyl ketones were very low in favour of a self-aldol product.[20a] Yet, in the absence of LiBr, fragmentation of **4a** with Et_3N in the presence of benzaldehyde resulted in isolation of the difluoromethyl ketone **5a** with no competing aldol reaction, with benzaldehyde being reisolated after reaction (eq. 4).

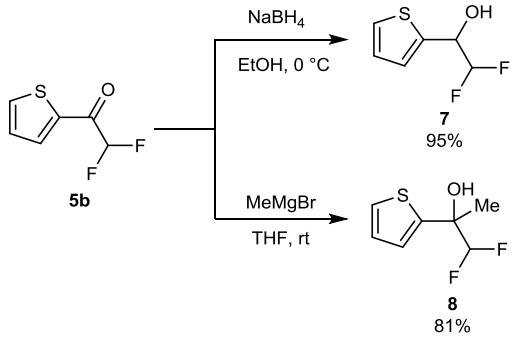


Future work will focus on delineating the role of Li salts in these aldol processes and the nature of any enolates formed in the presence and absence of Li salts.

We sought to finally demonstrate the usefulness of difluoromethyl ketones as building-blocks for the synthesis of more complex functional molecules. We showed that the thiophene- substituted difluoromethyl ketone **5b** underwent nucleophilic addition processes typical of ketones including reduction and Grignard addition to form difluoromethylated alcohols in very high yields (Scheme 4).

Conclusions

In this communication we have reported the first general, high-yielding route for the synthesis of difluoromethyl ketones, through a one-pot difluorination / fragmentation of 1-trifluoromethyl-1,3-diketones which proceeds through the base-mediated loss of trifluoroacetate. We hope this work will allow the potential of difluoromethyl ketones as useful building-blocks in medicinal and materials chemistry, as well as other areas, to be fully realized.



Scheme 4: Reactions of difluoromethyl ketone 5b

Acknowledgements

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