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Functionalization of 1,2-diphenylpyrazolidine-3,5-dione with polyfluoroalkyl-containing 2- and 3-oxo esters

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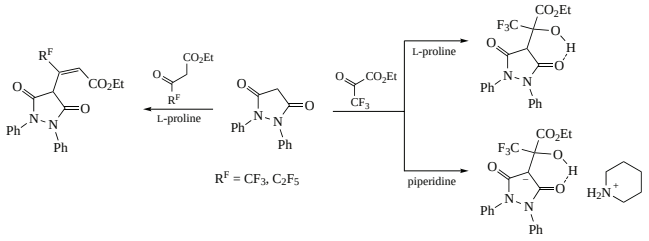
Fluorine-containing analogues of non-steroidal anti-inflammatory drugs Tribuzone and Ketazone have been synthesized by reaction of 1,2-diphenylpyrazolidine-3,5-dione with polyfluoroalkyl-containing 3- and 2-oxo esters. Ethyl 3-(pyrazolidin-4-yl)-3-(polyfluoroalkyl)prop-2-enoates have been obtained as Knoevenagel reaction products from 3-oxo esters in the presence of L-proline. Unlike with 3-oxo esters, addition of ethyl 3,3,3-trifluoro-2-oxopropanoate under basic conditions afforded ethyl 2-(pyrazolidin-4-yl)-3,3,3-trifluoro-2-hydroxypropanoate or its salt without elimination of a water molecule.



Keywords: Knoevenagel reaction, 1,2-diphenylpyrazolidine-3,5-dione, polyfluoroalkyl 3-oxo esters, polyfluoroalkyl 2-oxo esters, non-steroidal anti-inflammatory drugs.

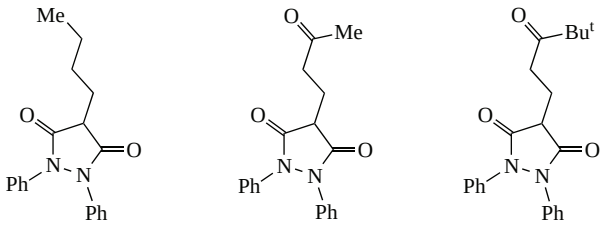
Anesthetic and non-steroidal anti-inflammatory drugs (NSAIDs) represent the most widely used and the best-selling pharmaceuticals, both in quantitative and monetary terms. However, a relatively high probability of side effects limits their use. For that reason, the development of new efficient NSAIDs with negligible adverse action remains a relevant goal.

Analysis of the chemical structures of NSAIDs employed in clinical practice has shown that many of them, along with a scaffold of salicylate, imidazole, pyrazole or propionic acid type, contain as well fluorine atoms. The fluorine-containing drugs typically possess greater bioactivity and lower toxicity. In fact, Diflunisal having a structure of acetylsalicylic acid with 2,4-difluorophenyl substituent at the 5-position is four times more active than aspirin in terms of anti-inflammatory effect and less erosive for the mucous membrane of gastrointestinal tract.[1] Flumizole is yet another example of fluorine-containing NSAID,[2,3] and its anti-inflammatory activity is two times higher than that of Phenylbutazone. The efficacy of Flumizole originates from its more lipophilic character compared with Phenylbutazone, which favors easier penetration through the blood–brain barrier.

The known NSAID Celecoxib[4,5] as well as anti-arthritis veterinary agent Mavacoxib[4] represent derivatives of 3-trifluoromethylpyrazole. These drugs selectively inhibit cyclooxygenase-2, whereas structurally similar non-fluorinated 4-(5-phenyl-3-methyl-1*H*-pyrazol-1-yl)benzenesulfonamide lacks the inhibitory activity toward both cyclooxygenase-1 and -2 isozymes.[4] The reason for the difference consists in the unique properties of fluorine atoms, which change the range of biological action for organic molecules and increase their biochemical and metabolic stability as well as lipophilicity.[6,7]

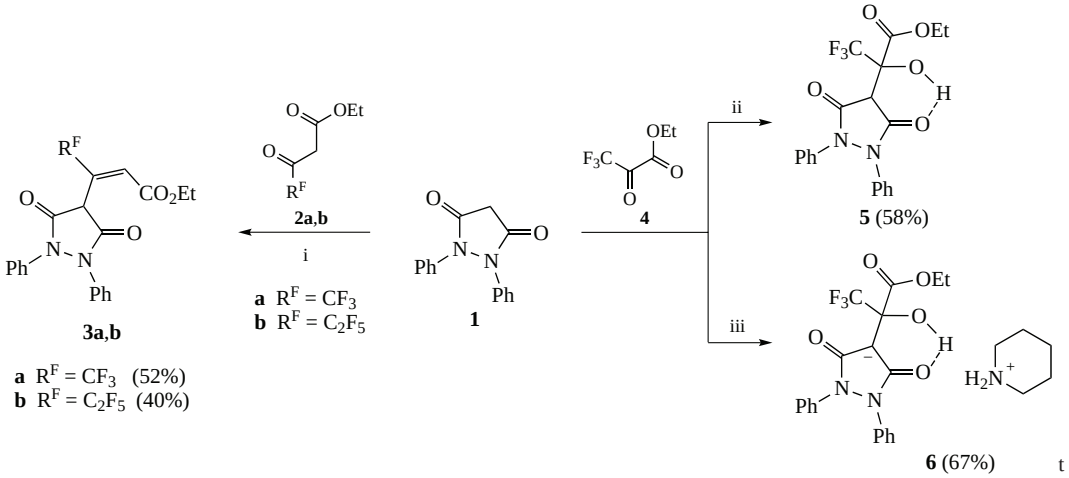
The intensive investigation of fluorine-containing pyrazole derivatives to search for new anti-inflammatory drugs[8–11] as well as to explore other types of their bioactivity[12,13] and magnetic properties of the corresponding coordination compounds[14] is currently in progress.

Our synthetic plan was based on fluorine-free 4-butylpyrazolidinone scaffolds of three known drugs, namely Phenylbutazone, Tribuzone and Ketazone, which possess analgesic, antipyretic as well as anti-inflammatory properties and are typically prescribed against rheumatoid arthritis, ankylosing spondylitis or arthrosis. They reduce the aggregation of thrombocytes, enhance fibrinolysis and also prevent severe gout complications.[15,16] However, Phenylbutazone and its analogues are characterized by a variety of contraindications, for example in patients with peptic ulcer of stomach and duodenum, blood-forming organs diseases, asthma, impaired liver or kidney function as well as heart rhythm disorders.



Phenylbutazone (Butadion) | Ketazone | Tribuzone

Synthesis of the fluorinated structural analogues of Tribuzone and Ketazone was carried out in this work *via* reactions of 1,2-diphenylpyrazolidine-3,5-dione **1** with polyfluoroalkyl-containing oxo esters **2a**,**b** and **4**. It was found that compound **1** underwent the Knoevenagel condensation with 3-oxo esters **2a**,**b** in the presence of L-proline as a catalyst affording ethyl

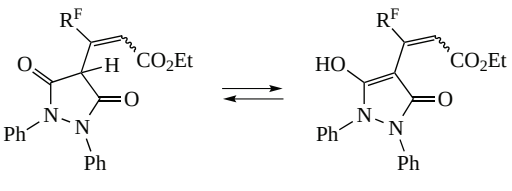


Scheme 1 *Reagents and conditions*: i, L-proline, benzene, 50–60 ºC, 12–18 h; ii, L-proline, benzene, room temperature, 3 h; iii, piperidine, benzene, 80 ºC, 1 h.

3-(3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)-3-(polyfluoroalkyl) prop-2-enoates **3a**,**b** (Scheme 1).†

It was established as well that for products **3a**,**b** the existence of *E*-isomers is preferable. In fact, pyrazolidinone **3a** with CF_3 group is detected by ^{1}H and ^{19}F NMR spectroscopy in DMSO-d_6 as an *E*/*Z* isomeric mixture in 97 : 3 ratio, while heterocycle **3b** with more bulky C_2F_5 substituent exists exclusively as the *E*-isomer. To assign the signals of *E*- and *Z*-isomers, we compared ^{19}F NMR spectra of compounds **3a**,**b** with known data.[17] The CF_3 group ^{19}F NMR signal in DMSO-d_6 for the *E*-isomer of compound **3a** is observed at 99.04 ppm, while for the *Z*-isomer the same group signal is located at 104.27 ppm relative to C_6F_6 (for details, see Online Supplementary Materials). This is in good agreement with the lower fluorine chemical shift of CF_3CH=CH moiety in (*E*)-(4,4,4-trifluorobut-2-enyloxymethyl) oxirane and (*E*)-11,11,11-trifluoro-1,2-epoxyundec-9-ene compared with their *Z*-counterparts, after the CF_3 groups shifts for these compounds have been recalculated relative to C_6F_6.[17]

Heterocycles **3a**,**b** have a moving proton at the 4-position of the pyrazole ring (diketone form **A**), which can be involved in tautomeric equilibrium with the enol form **B** (Scheme 2). We assume that in DMSO-d_6 heterocycles **3a**,**b** exist in the form **A** for the following reasons. Their ^{13}C NMR spectra contain one singlet of two amide carbonyl carbon nuclei in the range of 164.08–164.35 ppm and the signal of C-4 carbon nucleus at 80.37–80.42 ppm. In the ^{1}H NMR spectra, the signal of H-4 proton is observed as a broadened singlet at 7.91 and 4.35 ppm for compounds **3a** and **3b**, respectively. The downfield shift of H-4 proton for heterocycle **3a** may originate from a stronger electron-acceptor effect of its CF_3 group compared with the CF_2 group of product **3b**. Besides, the signals of methine atoms in R^FC=CH group, namely δ_C ~122.22–124.47 ppm and δ_H ~6.22–6.28 ppm in the corresponding ^{13}C and ^{1}H NMR spectra are broadened probably due to a long-range coupling with the fluorine nuclei.



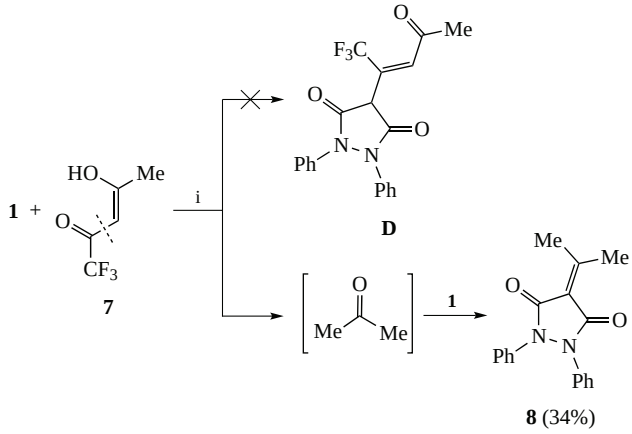
Scheme 2

The attempted Knoevenagel reaction of pyrazolidinedione **1** with ethyl 3,3,3-trifluoro-2-oxopropanoate **4** in the presence of L-proline or piperidine as a base stops at the stage of ester **4** addition to the activated methylene moiety of pyrazolidinone **1**, without subsequent elimination of a water molecule, affording adducts **5** or **6**, respectively (see Scheme 1).† Piperidinium salt **6** represents the final reaction product, when an equimolar amount of more basic piperidine is used as the base. Further attempts to dehydrate compounds **5** and **6** into Knoevenagel condensation products failed.

The ^{19}F NMR signals of CF_3 groups in heterocycles **5** and **6** are observed at ~85 ppm, which indicates their attachment to an sp^3-hybridized carbon atom. The signal of H-4 proton in product **5** appears as a broadened singlet at 7.07 ppm. The IR spectrum of compound **5** contains two high-intensity maxima at 1766 (CO_2Et) and 1728 cm^{-1} (C=O), in contrast to the spectrum of salt **6** with only one carbonyl maximum at 1740 cm^{-1}.

Note that our attempts to engage ethyl acetoacetate into the Knoevenagel reaction with pyrazolidinedione **1** under similar conditions failed. The ability of esters **2a**,**b** and **4** to enter this reaction is due to higher electrophilicity of the carbonyl carbon atom bearing a polyfluoroalkyl substituent.

The structures of Tribuzone and Ketazone as representatives of NSAIDs contain ketone side chains, namely 4,4-dimethyl-3-oxopentyl and 3-oxobutyl, respectively, at the 4-position of the pyrazole ring. To obtain a fluorinated analog with a similar ketone side chain, we explored the reaction of pyrazolidinedione **1** with 1,1,1-trifluoropentane-2,4-dione **7**. It is known[18] that in the presence of proline, compound **7** undergoes an 'acid



Scheme 3 *Reagents and conditions*: i, L-proline, benzene, 40 °C, 12 h. The acid cleavage site of compound **7** is indicated by dashed line.

† For details of the synthesis and characteristics of heterocycles **3a**,**b**, **5** and **6**, see Online Supplementary Materials.

cleavage.' We assumed that products of the cleavage could be trifluoroacetamide and acetone. Therefore, the addition of intermediate acetone to the activated methylene moiety of compound **1** followed by elimination of a water molecule afforded 1,2-diphenyl-4-isopropylidenepyrazolidine-3,5-dione **8** (Scheme 3). Note that heterocycle **8** had been obtained by the reaction of acetone with pyrazolidinedione **1** in the presence of 3Å molecular sieves.[19] Our monitoring of the process by GC–MS analysis of aliquots taken from the reaction mixture did not reveal even traces of anticipated condensation product **D** (see Scheme 3).

In summary, 1,2-diphenylpyrazolidine-3,5-dione has been modified at its 4-position by reaction with polyfluoroalkyl-containing 3-oxo esters affording ethyl 3-(3,5-dioxo-1,2-diphenylpyrazolidin-4-yl)-3-(polyfluoroalkyl)prop-2-enoates and with a trifluoromethyl-containing 2-oxo ester resulting in the corresponding hydrated adducts. However, attempted similar reaction with 1,1,1-trifluoropentane-2,4-dione as a fluorinated 1,3-diketone led to 1,2-diphenyl-4-isopropylidenepyrazolidine-3,5-dione due to condensation of the starting pyrazolidine with acetone formed after 'acid cleavage' of the 1,3-diketone. The heterocycles obtained are promising for further biological tests as potential NSAIDs.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.026.

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