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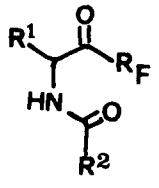
SYNTHESIS OF FLUORINATED α-AMINO KETONES.
PART II: α-ACYLAMINOALKYL α',α'-DIFLUOROALKYL KETONES

Michael Kolb* and Bernhard Neises
Merrell Dow Research Institute, Strasbourg Center
16 rue d'Ankara, 67084 Strasbourg Cedex, France

Abstract: The synthesis of α-acylaminoalkyl 1.1-difluoro-3-butenyl ketones 2 is described. Reaction of substituted 5(4H)-oxazolones 4, obtained from α-amino acids, with 2.2-difluoro-4-pentenoic acid anhydride 3 (for $R^2 = C_6H_5$) or with 2.2-difluoro-4-pentenoic acid chloride 7 and 4-dimethylaminopyridine / triethylamine [for $R^2 = CH_3$, C_6H_5, $CH(CH_2C_6H_5)NHCO_2CH_2C_6H_5$] followed by treatment with anhydrous oxalic acid gives the target structures 2.

Earlier we reported on a practical synthesis of α-benzamidoalkyl mono-, di- and trifluoromethyl ketones 1, starting from α-amino acids[1]. With as objective the use of this set of functional groups in our research program directed towards the inhibition of proteases[2], a more flexible substitution pattern at the fluorinated carbon atom was desirable.

We now report on the synthesis of α-acylaminoalkyl 1.1-difluoro-3-butenyl ketones 2, compounds which incorporate all the features necessary to allow further elaboration of the fluorinated part of the ketone structure for the aforementioned purpose[3].

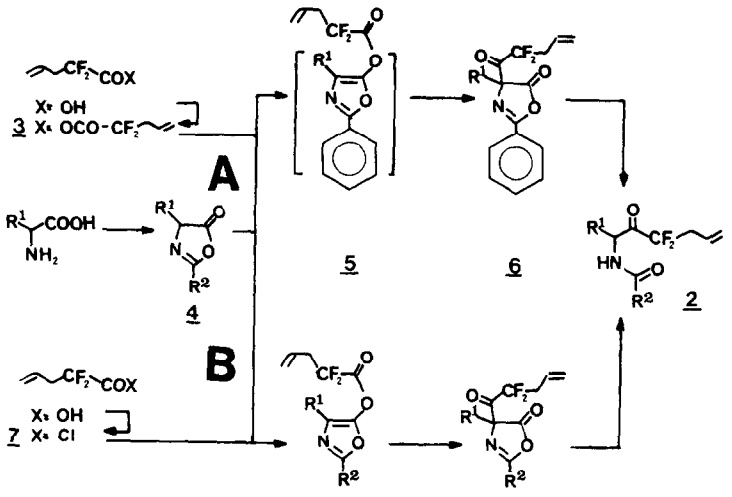


1 $R_F = CF_3$, CF_2H, CFH_2; $R^2 = C_6H_5$
2 $R_F = CF_2-CH_2-CH=CH_2$

Access to ketones 2 relies on the experience gained in the earlier syntheses of the fluorinated methyl ketone analogues 1[1] via a modified Dakin-West procedure[4]. Reaction of one equivalent of 2.2-difluoro-4-pentenoic acid anhydride 3[5], obtained from the corresponding acid[6] via its silver salt[7] (oxalyl chloride,CH_2Cl_2,0°C → 20°C;then 40°C for 30 min;yield 75%;b.p.78-80°C / 20 Torr), with the oxazolones 4 ($R^2 = C_6H_5$)[8] at 60°C (oil bath temp.) for 20 h under nitrogen atmosphere affords the C-acylated[9] compounds 6 (Scheme 1,route **A**). Removal of 2.2-difluoro-4-pentenoic acid, formed during the reaction, and residual anhydride 3 (60°C, oil bath temp., 0.01 Torr) gives the crude oxazolones 6 as oils, which are treated with anhydrous oxalic acid (1 equiv,110-120°C,oil bath temp.,15 min) to achieve decarbonylation. After work-up (EtOAc/water,conc.$NaHCO_3$,brine;dried over $MgSO_4$) the fluorinated α-benzamidoalkyl ketones 2

(R^2= C_6H_5) are isolated in satisfying yield (Table 1) with the exception of entry 1. The meagre yield obtained for this glycine derived ketone 2 (R^1= H,R^2= C_6H_5), we ascribe to the instability of the corresponding oxazolone 4 under the reaction conditions[10].

Scheme 1



The convenience of this reaction pathway is tempered by two constraints:

1.The scope of the sequence seems to be narrow and only α-benzamidoalkyl ketones could be obtained directly from the corresponding oxazolones 4 (R^2= C_6H_5)[11].

2.The necessity to use the anhydride 3 of the non-commercial 2.2-difluoro-4-pentenoic acid spoils the otherwise efficient conversion of the fluorinated reaction partner into the products.

A potential solution to the former obstacle arises from a related series of compounds where it could be shown that the strategy of functional group manipulation allows for the synthesis of other α-acylaminoalkyl di- and trifluoromethyl ketones 2 (R^2 not C_6H_5)[3].

A more general modus operandi which takes into account not only our desire for flexibility in the choice of the acyl group at the nitrogen atom but also improves on the latter problem is described below.

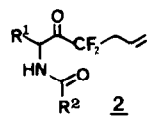
The use of acid chlorides instead of anhydrides in the Dakin-West reaction in combination with base and an acylating catalyst is well documented in the literature[12]. Although the addition of triethylamine and 4-dimethylaminopyridine is deleterious to the outcome of the reaction of trifluoroacetic anhydride with oxazolones 4[13], these reagents were found to be beneficial in our attempt to use 2.2-difluoro-4-pentenoic acid chloride 7 in the sequence towards the target ketones 2 (Scheme 1,route B)[14].

To a mixture obtained from the reaction of 5(4H)-oxazolones 4 with Et_3N (1.2 equiv,5 min) in THF at -5 to 0°C under nitrogen atmosphere is added dropwise a freshly prepared solution of 2.2-difluoro-4-pentenoic acid chloride 7 (1.2 equiv) in hexane[15](external ice cooling,0°C). The reaction is complete after stirring for further 1 h at 20°C. The mixture is filtered and the

filtrate evaporated thoroughly (0.05 Torr,14 h). The crude O-acylated oxazoles 5[16] (Scheme 1) are then diluted with THF (about 0.2 mL/mmol) and 4-dimethylaminopyridine (0.1 equiv) is added. Stirring for 2 h at 20°C allows for the rearrangement of the O-acylated derivative 5 to the C-acylated species 6 (monitored by ^{19}F-NMR[9,16]). Removal of the solvents gives crude oxazolones 6 which are decarbonylated smoothly by treatment with a saturated solution of anhydrous oxalic acid in THF (2 equiv,14 h,20°C). Work-up (AcOEt/water,conc. $NaHCO_3$,N HCl,brine;dried over $MgSO_4$) affords the fluorinated α-acylaminoalkyl ketones 2, which then can be purified by chromatography on silicagel to yield analytically pure α-acylaminoalkyl 1.1-difluoro-3-butenyl ketones 2 in satisfying yield (Table 1).

Table 1

Yield, m.p., and ^{19}F-NMR data for the α-acylaminoalkyl 1.1-difluoro-3-butenyl ketones 2

 2		Yield[a] [%]	m.p. [°C]	^{19}F-NMR δ_{CFCl_3} [ppm][b] solvent: $CDCl_3$,C_6F_6	
R^1	R^2			δ_{CFCl_3} F_A	δ_{CFCl_3} F_B
FROM ANHYDRIDE					
1 H		15[c]	55-57	-108.3/-115.3[d]	
2 i-C_4H_9	C_6H_5	73	45	-103.5	-110.5
3 C_6H_5-CH_2		60	98	-103.7	-110.7
FROM ACIDCHLORIDE					
4 i-C_4H_9		46	44-45	-103.5	-110.5
5 C_6H_5-CH_2	C_6H_5	38	97-98	-103.7	-110.7
6 p-NO_2-C_6H_4-CH_2		40	152-154	-102.5	-109.5
7 CH_3O_2C-NH-$(CH_2)_4$		54	76-77	-103.8	-110.8
8 i-C_4H_9	ZNH-$(C_6H_5CH_2)$CH[d]	53	oil	-103.2	-110.2
9 C_6H_5-CH_2	CH_3	20	50-51	-103.5	-110.5

a: Not optimized yield of analytically (CHN) pure compounds; b: But for entry 1 (see d), all spectra show an ABX_2 pattern, $^2J_{FAFB}$= 270 Hz, J_{FAHX}= 17 Hz= J_{FBHX}; c: see text; d: 2t, (96:4), interpreted as the ketone 2(R^1= H, R^2= C_6H_5) and its hydrated form; e: Z= benzyloxycarbonyl.

The difluoro ketone derivatives 2 were, with the exception of the dipeptide analogue described in entry 8, isolated as colourless, solid materials. As judged from the ^{19}F-NMR data (see Table 1) the reaction products 2 were obtained in general in the ketone form; only for the glycine derived difluoro ketone described in entry 1, we observed some hydrated species in the final compound.

Unlike the anhydride sequence which seemingly is limited to benzamido derivatives 2 (R^2= C_6H_5), the acid chloride pathway permits different groups in position 2 of the 5(4H)-oxazolone structure 4. Not only phenyl (entries 4 - 7), but also methyl (entry 9) and other functionalized alkyl groups (entry 8) are compatible with the reaction conditions[17]. The fact that the acid chloride approach is also useful when, instead of α-amino acids, peptides are considered as suitable starting materials (entry 8) deserves special note[18,19].

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5. H-NMR ($CDCl_3$,TMS)δ 6.0-5.5(m,1H,=CH-),5.45 and 5.25(2m,2H,=CH_2),2.95(dt,2H,J_{FH}=17Hz,J_{HH}=7.5 Hz,CF_2-CH_2); ^{19}F-NMR($CDCl_3$,C_6F_6)δ($CFCl_3$)-107.0(t,J_{FH}=17Hz).
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7. Prepared by addition of a solution of 2.2-difluoro-4-pentenoic acid[7] in water to Ag_2O/water.
8. Obtained by standard procedures from the corresponding α-amino acids: W. Steglich, Fortschr. Chem. Forsch. 12/1, 77 (1969); E. Carter, Org. React. 3, 198 (1949).
9. ^{19}F-NMR($CDCl_3$,C_6F_6)δ($CFCl_3$)-104.7±0.1 for the C-acylated compound 6. Careful monitoring of the progress of the anhydride reaction by ^{19}F-NMR spectroscopy allows to identify the presence of an intermediate compound between the starting oxazolone 4 and of the C-acylated reaction product 6. The chemical shift of the additionally observed ^{19}F-NMR signals allows us to attribute structure 5 to this intermediate (see lit.[16]).
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11. The use of oxazolones 4 where R^2 is CH_3 or $CH(CH_2C_6H_5)NHCO_2CH_2C_6H_5$ under the reaction conditions employed in the anhydride sequence gave no C-acylated products 6.
12. W. Steglich, G. Höfle, Chem. Ber. 102, 883 (1969) and literature cited therein.
13. J. Lepschy, PhD thesis, Technische Universität München, 1971.
14. Instead of the acid chloride 7, the anhydride 3 can in principle be used too. This was verified by the synthesis of 1-benzamido-2-phenylethyl 1',1'-difluoro-3'-butenyl ketone 2 under the conditions described for the acid chloride procedure.
15. The acid chloride is obtained from the corresponding acid[7] by treatment with oxalyl chloride in n-hexane and a catalytic amount of DMF: ^{19}F-NMR(nC_6H_{12},C_6F_6)δ($CFCl_3$)-105.0 (t,J_{FH}=18Hz).
16. ^{19}F-NMR($CDCl_3$,C_6F_6)δ($CFCl_3$)-108.6±0.4 for the O-acylated compound 5.
17. An attempt which used the N-formyl derivative (R^2= H) failed.
18. We are aware of only one other example for the use of an acid chloride in the Dakin-West reaction with peptides, which is reported in lit. 12.
19. Anhydrides as reaction partner in the Dakin-West reaction with peptides are used in some examples: G.Höfle, W.Steglich, H. Vorbrüggen, Angew. Chem. Int. Ed. 17, 569 (1978); S. Fitkau, G. Jahreis, J. Prakt. Chem. 326, 48 (1984); J. S. McMurray, D. F. Dyckes, J. Org. Chem. 50, 1112 (1985); D. Rasnick, Anal. Biochem. 149,461 (1985), Europ. Pat. Appl. 85-013893, 17. 05. 1984; see also lit. 12 .

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