Tetrahedron Letters,Vol.27,No.14,pp 1579-1582,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF FLUORINATED α-AMINO KETONES
PART I: α-BENZAMIDOALKYL MONO- DI- AND TRIFLUOROMETHYL KETONES

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2-Phenyl-5(4H)-oxazolones, obtained from α-amino acids, are reacted with di- and trifluoro acetic anhydride by a modified Dakin-West procedure to yield in a one-pot reaction α-benzamidoalkyl-di- and trifluoromethyl ketones in good yields. The monofluoromethyl analogues were also prepared from α-amino acids, however the use of the highly toxic fluoroacetic anhydride was avoided. The key step is the halogen exchange reaction on the corresponding bromomethyl ketone.

In the context of our research efforts directed towards the synthesis of protease inhibitors, an easy and suitable access to α-amino α'-fluorinated ketones became mandatory. A literature survey revealed the scarcity of reports on this array of functional groups. The synthesis of the hydrate of 1-benzamido-3,3,3-trifluoro-2-propanone from glycine, described in 1961 by Tatlow[1] is the earliest reference on this subject. The authors had no success in their attempts to enlarge the scope of their reaction scheme.

Ten years later, Steglich's group reinvestigated the problem[2], and described in a thesis a modified Dakin-West procedure for the synthesis of three more examples of α-benzamidoalkyl trifluoromethyl ketones.

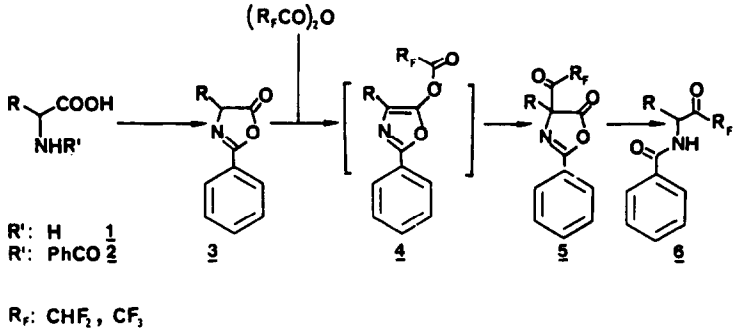
Only recently, the Reformatsky reaction[3] was used be several authors[4] in the synthesis of α-acylaminoalkyl-α',α'-difluoro-β'-oxoalkyl ketones; and even more recent[5] is the use of α-nitro carbanion chemistry in the synthesis of the title structures[6,7].

We considered the Dakin-West reaction[8,9] as general and therefore the most attractive entry to fluorinated amino ketones. However, as already reported in the literature[1,2,6], typical Dakin-West reaction conditions are restricted in this context to the monofluoromethyl series or to glycine as reaction partner on the amino acid side.

Inspired by the work reported in the thesis from Steglich's group, we now describe a convenient and practical method for the synthesis of α-benzamidoalkyl di- and trifluoromethyl ketones from α-amino acids as starting material. The sequence relies on the Dakin-West procedure to the extent that the anhydrides of di- and trifluoroacetic acid are reacted with 2-phenyl-5(4H)-oxazolones 3, obtained from the corresponding amino acids 1. However, well-defined reaction conditions have to be met in order to obtain the desired fluorinated amino ketones. α-Amino acids 1 are N-benzoylated by standard techniques (NaOH, H_2O, Et_2O, C_6H_5COCl, pH = 10-12) and the benzamido derivatives 2 are then cyclised to the corresponding 2-phenyl-5(4H)-oxazolones 3 (Ac_2O)[10,11] (Scheme I). Reaction of the oxazolone 3 with the anhydrides of di- or trifluoroacetic acid (1.1 equiv.) is accomplished at 40 °C (oil-bath temperature) under N_2 atmosphere for 12-48 h (^{19}F-NMR monitoring). The direct conversion of the amino acid derivative 2 to the acylated oxazolone 5 is also feasible and exemplified by the

preparation of ketone 6g from N-benzoyl p-guanidinophenylalanine 1 [R = $p(H_2NC(=NH)NH)C_6H_4CH_2$; 15 equiv. of trifluoroacetic anhydride, 40 °C, 20 h]. When all starting material 3 is consumed, the C_4-acylated oxazolone 5 is the main product. Residual anhydride and the di- or trifluoroacetic acid formed are removed thoroughly under vacuum (50–80 °C oil-bath temperature, 0.01 Torr); the residue is mixed with anhydrous oxalic acid (sublimed twice, 1.5 equiv.) and the mixture is heated to 110–120 °C for 10–15 min, until all gas evolution has ceased. Work up ($EtOAc/H_2O$, aq. $NaHCO_3$, brine; dried over $MgSO_4$) gives in good to satisfactory yield the desired fluorinated ketones 6.

Scheme I



The scope of the reaction scheme is illustrated in Table 1. All of the isolated fluorinated benzamidoalkyl ketones 6 and 10 are stable colourless solids. In most cases, they represent mixtures of the hydrated and non-hydrated species at ratios which seem to be influenced by the steric (see the glycine product 6a vs the valine derived ketone 6b) and electronic (see the trifluoro ketone 6d vs the difluoro derivative 6j or the monofluorinated compound 10) environment[12]. Provided suitable protection is available, functionalized α-amino acids can be used also (see the benzyloxycarbonyl protected ketone 6i). In certain cases, the protection of the additional functional groups is unnecessary (see the functionalized aryl compounds 6e and 6g).

Limiting the versatility of the reaction scheme is the nature of the C-2 substituent of the oxazolone 3. In our hands[13], only 2-phenyl-5(4H)-oxazolones proved to be useful for the sequence outlined in scheme I, which limits the scope to α-benzamido derivatives[14].

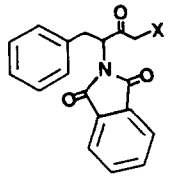
As already suggested[2], the reaction of the 5(2H)-oxazolones 3 with the fluorinated acetic anhydride to give the C-acylated derivative 5 seems to involve at least one intermediate. Careful examination of the ^{19}F-NMR spectra obtained at certain time intervals during the reaction allows one to observe a signal at $\delta_{CFCl_3} = -74.5$ preceeding in time the appearance of the fluorine signal attributed to 5 ($\delta_{CFCl_3} = -75.5$). With the latter then increasing at the expense of the earlier peak, it seems reasonable to assign the first signal to the intermediate O-acylated species 4.

Table 1: Yields and ^{19}F NMR Data of Benzamido Fluoro Ketones 6 and 10

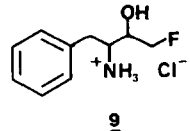
Ketone:				^{19}F NMR δ_{CFCl_3} ext. (ppm)			
N°	R	Rf	Yield [%][c]	[Solvent][a]	Ketone	Hydrate	Ratio
6a[1)]	H	CF_3	70	[A]	- 81.6	- 86.0	7:93
6b	i-C_3H_7		26	[B]	- 77.5		100:0
6c	i-C_4H_9		60	[B]	- 76.8	- 82.7	90:10
6d	C_6H_5-CH_2		63	[C]	- 76.6	- 82.4	20:80
6e	(p-NO_2)C_6H_4-CH_2		55	[B]	- 76.0	- 83.0	50:50
6f	(p-NH_2)C_6H_5-CH_2		-[e,f]	[B]		- 83.0	0:100
6g	[p-$H_2NC(=NH)NH$]C_6H_4-CH_2		53[f]	[D]		- 83.0	0:100
6h	$C_6H_5CH_2$-CH_2		49	[B]	- 78.2	- 83.3	83:17
6i	$C_6H_5CH_2OCONH$-$CH_2CH_2CH_2CH_2$		56	[B]	- 79.7	- 82.6	66:33
6j	$C_6H_5CH_2$	CF_2H	50	[E]	- 129.0[b]		100:0
6k	i-C_4H_9		22	[B]	- 120.0[b]		100:0
10	$C_6H_5CH_2$	CFH_2	-[d]	[B]	- 231.5		100:0

a: A = $CDCl_3/C_6F_6/(CD_3)_2CO$, B = $CDCl_3/C_6F_6$, C = $(CD_3)_2CO$/TFA, D = D_2O/DCL/TFA, E = $CDCl_3$/TFA; b: ABX center; c: calcd from 3; d: see text; e: obtained from 6e: Pd/C, H_2, AcOEt, HCl (yield 50 %); f: isolated as hydrochloride salts.

Our concern in devising a suitable route to the target structures mentioned above did not allow us to extend the above sequence to the monofluorinated analogues[15]. Therefore an alternative scheme was developed, which is based on a bromine/fluorine exchange reaction next to the ketone functionality. A solution of 3-phthalimido-1-bromo-4-phenyl-2-butanone (7)[16], obtained from phenylalanine[17], in acetonitrile and KF/18-crown-6 was refluxed for 30 h[18] to produce the fluoromethyl analogue 8 (yield 45 %). Reduction of the ketone ($NaBH_4$, EtOH) allows the removal of the phthaloyl group (N_2H_4, H_2O, EtOH, HCl) in order to obtain the aminoalcohol hydrochloride 9 in 50 % overall yield from 8. N-Benzoylation (C_6H_5COCl, NaOH, Et_2O, pH = 10-12, 43 %) followed by oxidation of the hydroxy function (Swern[19]) then gave the target structure 10.



X: Br 7
X: F 8



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REFERENCES

1. E.J. Bourne, J. Burdon, V.C.R. McLoughlin, J.C. Tatlow, J. Chem. Soc., 1961, 1771.
2. J. Lepschy, Ph.D. thesis, Technische Universität München, West Germany, 1971.
3. E.A. Hallinan, J. Fried, Tetrahedron Lett., 25, 2301, 1984.
4. S. Thaisrivong, D.T. Pals, M.W. Kati, S.R. Turner, L.M. Thomasco, J. Med. Chem., 28, 1555, 1985; M.H. Gelb, J.P. Svaren, R.H. Abeles, Biochemistry, 24, 1813, 1985.
5. B. Imperial, R.H. Abeles, Tetrahedron Lett., 27, 135, 1986.
6. Recently D. Rasnick reported the synthesis of two monofluoromethyl analogues, employing the anhydride of the extremely toxic fluoroacetic acid[15]: Eur. Pat. Appl. 85-013893, 17 May 1984; Anal. Biochem., 149, 461, 1985.
7. For N-aroylphenylaminotrifluoroaceton see G. Singh, S. Singh, Tetrahedron Lett., 1964, 3789.
8. H.D. Dakin, R. West, J. Biol. Chem., 78, 91, 1928.
9. W. Steglich, G. Höfle, Angew. Chem. Int. Ed., 8, 981, 1969.
10. W. Steglich, Fortschr. chem. Forsch., 12/1, 77, 1969; H.E. Carter, Org. Reactions, III, 198; "The Chemistry of Penicillin", Ed. H.T. Clarke, J.R. Johnson, Sir R. Robinson, Princeton Univ. Press, Princeton New Jersey, 1949, p 730.
11. New are: 2-phenyl-4-[(4-nitro)phenylmethyl]-5(4H)-oxazolone 3e: (R = p-NO_2-$C_6H_4CH_2$): m.p. 147-148 °C, Anal. Calcd for $C_{16}H_{12}N_2O_4$ (296.29): C, 64.86; H, 4.08; N, 9.46. Found: C, 64.59; H, 4.11; N, 9.54.
    2-phenyl-4-phenylethyl-5(4H)-oxazolone 3h: (R=$C_6H_5CH_2CH_2$): m.p. 103-105 °C, Anal. Calcd for $C_{17}H_{15}NO_2$ (265.32): C, 76.96; H, 5.70; N, 5.28. Found: C, 77.38; H, 5.86; N, 5.29.
12. A more detailed investigation on the nature of the effects influencing the ketone/hydrate ratio in this series of compounds will be reported elsewhere.
13. Unsuccessful attempts were made to replace the phenyl substituent by benzyloxy, methyl or hydrogen.
14. This problem is addressed in detail in Part II of this series: M. Kolb, B. Neises, Tetrahedron Lett., manuscript in preparation.
15. For toxicity of fluoroacetic acid see: The Merck Index, 10th Ed., 1983, p 597.
16. H-NMR ($CDCl_3$): δ 7.9-7.7(m,4H,phthaloyl);7.2(narrow m,5H,aryl);5.43(dd,1H,J=6 and 2 Hz,NCH);4.00(s,2H,CH_2Br);3.50(ABX,2H,J=15, 6 and 10 Hz,CH_2);IR($CHCl_3$) 1780 and 1720 (carbonyl) cm^{-1};MS(EI) m/e 373 and 371 (M^+,15%);250 (100%); 232 (50%).
17. Via acid chloride and diazoketone (B. Penke, J. Czombos, L. Balaspiri, J. Peters, K. Kovacs, Helv. Chim. Acta, 53, 1057 (1970)) to bromomethyl ketone (via the general procedure described in "Organikum", VEB Verlag der Wissenschaften, Berlin 1968, p. 531): 65 % overall yield from N-phthaloyl phenylalanine.
18. Analogous to K.M. Move, J. Wemple, Synthesis, 1977, 791.
19. A.J. Mancuso, S.L. Huang, D. Swern, J. Org. Chem., 43, 2480, 1978.

(Received in France 10 February 1986)