A NEW AND EFFICIENT SYNTHESIS OF 4-ARYLIMIDAZOLIDIN-2-ONES

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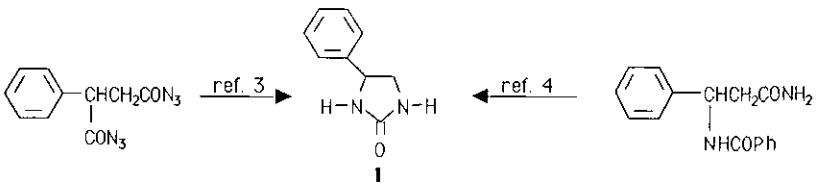
Abstract ------*Curtius rearrangement of 3-trifluoroacetylamino-3-arylpropionyl azides gave 4-aryl - imidazolidin-2-ones via an anchimeric assistance reaction.*

Although imidazolidine-2,4-diones (hydantoïnes) have focused numerous chemical and pharmaceutical works, on the other hand imidazolidin-2-ones which nevertheless possess potent biological interest[1] have been less studied. This lack of interest is probably due to the fact that no effective and versatile approach is available.

We wish to report herein a facile and efficient synthesis of title compounds which turns in account an anchimeric assistance reaction of a trifluoroacetyl group towards isocyanates generated during Curtius rearrangement of N-trifluoroacetyl protected 3-amino-3-arylpropionyl azides. Our recent studies on the reactivity of these N-protected β-amino acids have yet pointed out the particular character of the trifluoroacetyl protecting group which for example facilitates the cyclization of cyclopentanes[2] or promotes the formation and the cleavage of aziridines via neighbouring group effect.[3]

Thus in order to prepare new 4-arylimidazole derivatives we have reinvestigated the synthesis of 4-phenylimidazolidin-2-one previously described by Curtius[4] or Kanewskaja[5] who prepared this compound either by the double rearrangement of phenylsuccinyl azide or by Hoffman rearrangement of 3-benzoylamino-3-phenylpropionamide.
(Scheme 1)



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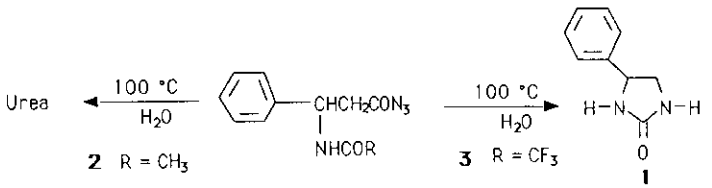
Scheme 1

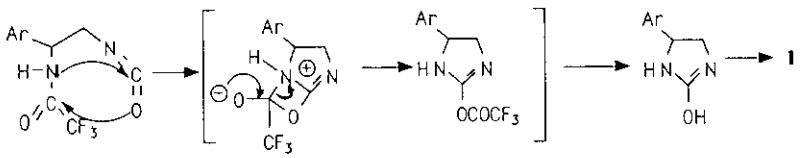
With the view to simplify these routes we have submitted 3-acetylamino- or 3-trifluoroacetylamino-3-phenylpropionyl azides (2) and (3) to Curtius rearrangement and observed quite different comportments.

The N-acetyl derivative (2) lead in refluxing water to the expected symmetric urea without reaction between the intermediate isocyanate and acetamido group.
In the same conditions starting with the trifluoro derivative (3) a preferential intramolecular cyclization took place and the reaction conducted to the exclusive formation of the 4-phenylimidazolidin-2-one (1) in high yield. (Scheme 2)



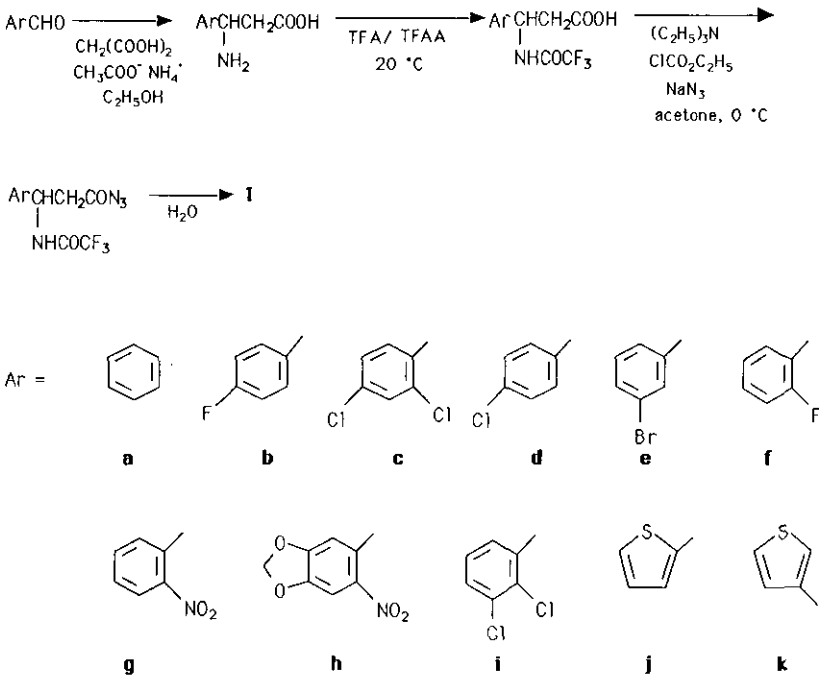
Scheme 2

This intramolecular cyclization must be considered as the consequence of an anchimeric assistance reaction of the trifluoroacetamido group which results from a double attack between the latter and the isocyanate group. One can suggest a four centers concerted mechanism which is possible on account of the great electrophilic character of the C atom of the trifluoroacetyl carbonyl which authorizes the formation of a tetrahedric intermediate conducting to a trifluoroacetate which is finally hydrolyzed. (Scheme 3)



Scheme 3

We have applied with success this reaction to 11 examples (substituted phenyl and 2- or 3-thienyl derivatives) and we obtained the corresponding imidazolidinones (**1a-k**) with high yields; however surprisingly this reaction failed with 2-furyl derivative.
In conclusion this particular reaction permits a facile route to the title compouds in four steps starting with aryladehydes according to the following Scheme 4.



Scheme 4

EXPERIMENTAL

Melting points were determined on a Kofler bank and are uncorrected. Infrared spectra were measured on a Philips PU 9716 apparatus. Nmr spectra were recorded on a Jeol FX 200 operating at 199.9 MHz for ^1H.

4-Arylimidazolidin-2-ones (1a-k) : general procedure.

To a stirred ice cold solution of 3-aryl-3-trifluoroacetylaminopropionic acid [1a] (1. 0 mmol) in acetone (20 ml) triethylamine (0. 2 ml, 1. 1mmol) was added, after 30 min ethyl chloroformate (0. 1ml, 1. 0 mmol) was slowly added at such a rate that the temperature was kept between 0°C and 5°C, and then after 30 min a water solution (5ml) of sodium azide (7mg, 1. 1 mmol) was added at the same temperature. The reactionnal mixture was finally stirred for 1 h, poured into water (60 ml) and extracted twice with chloroform (2 x 30 ml). The organic layer was washed with water (3 x 60 ml), and concentrated to a third of its volume under reduced pressure at room temperature. Water (50ml) was then added to this solution of azide and the well stirred resulting mixture was heated at reflux temperature for 30 min. Chloroform was evaporated and after cooling the white crystalline precipitate was collected by suction, washed with cold water, and dried.

Table 1 Spectroscopic data of compounds (1a-k)

Compd No	Ir (KBr) υ_{max} (cm^{-1})	^{1}HNmr (DMSO-d_6) δ ppm / TMS
1a	3200(NH) 1720(C=O)	7. 31(m, Ar); 6. 81(s, NH); 6. 70(s, NH); 4. 72(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 69(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 00(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1b	3200(NH) 1720(C=O)	7. 36(m, Ar); 6. 80(s, NH); 6. 30(s, NH); 4. 80(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 73(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 00(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1c	3200(NH) 1720(C=O)	7. 53; 7. 43(m, Ar); 6. 80(s, NH); 6. 30(s, NH); 4. 93(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 80(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 2. 93(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1d	3200(NH) 1720(C=O)	7. 00(m, Ar); 5. 10(s, NH); 4. 83(s, NH); 4. 57(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33Hz, H-4); 3. 60(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 00(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1e	3220(NH) 1680(C=O)	7. 49; 7. 42 ; 7. 29(m, Ar); 6. 86(s, NH); 6. 32(s, NH); 4. 74(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4) 3. 71(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 03(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1f	3200(NH) 1730(C=O)	7. 40; 7. 30(m, Ar); 6. 77(s, NH); 6. 43(s, NH); 4. 94(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 77(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 06(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1g	3210(NH) 1740(C=O)	8. 00(d, $J_{3',4'}$ = 6. 83 Hz, H-3'); 7. 80(d, $J_{6',5'}$ = 6. 83 Hz, H-6'); 7. 75(m, H-4'); 7. 58(m, H-5') 6. 83(s, NH) 6. 37(s, NH); 5. 08(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 85(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 09(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1h	3220(NH) 1720(C=O)	7. 66(s, H-3'); 7. 12(s, H-6'); 6. 87(s, NH); 6. 42(s, NH); 6. 26(s, CH_2); 5. 13(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 88(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 10(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1i	3200(NH) 1720(C=O)	7. 53(m, H-4'); 7. 43(m, H-5', H-6'); 6. 80(s, NH); 6.30(s, NH); 4. 83(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 80(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 2. 93(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1j	3300(NH) 1720(C=O)	7. 53(dd, $J_{5',4'}$ = 5. 20, $J_{5',3'}$ = 1. 5 Hz, H-5'); 7. 06(m, H-3', H-4', NH); 6. 47(s, NH); 5. 05(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 70(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 20(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)
1k	3200(NH) 1680(C=O)	7. 43(d, $J_{5',4'}$ = 5. 20 Hz, H-5'); 7. 30(s, H-2'); 7. 01(d, $J_{4',5'}$ = 5. 20 Hz, H-4'); 6. 72(s, NH); 6. 18(s, NH); 4. 72(dd, $J_{4,5a}$ = 7. 81, $J_{4,5b}$ = 7. 33 Hz, H-4); 3. 60(dd, $J_{5a,5b}$ = 15. 14, $J_{5a,4}$ = 7. 81 Hz, H-5a); 3. 10(dd, $J_{5b,5a}$ = 15. 14, $J_{4,5b}$ = 7. 33 Hz, H-5b)

Table 2

Compd No.	Yield (%)	mp (°C) (Solvt of cryst.)	Mol. Formula	Analysis (%) Calcd (Found)		
				C	H	N
1a	87	151 (H_2O)	$C_9H_{10}N_2O$	66.65 (66.54)	6.21 (6.10)	17.27 (16.98)
1b	70	170 (H_2O)	$C_9H_9N_2OF$	59.99 (60.10)	5.03 (4.97)	15.55 (15.67)
1c	86	210 (H_2O)	$C_9H_8N_2OCl_2$	46.78 (46.88)	3.49 (3.52)	12.12 (12.01)
1d	87	186 (H_2O)	$C_9H_9N_2OCl$	54.97 (54.77)	4.58 (4.49)	14.25 (13.99)
1e	80	172 (H_2O)	$C_9H_9N_2OBr$	44.84 (44.44)	3.76 (3.73)	11.62 (11.22)
1f	77	158 (H_2O)	$C_9H_9N_2OF$	59.99 (59.90)	5.03 (4.84)	15.55 (15.50)
1g	78	178 (H_2O)	$C_9H_9N_3O_3$	52.17 (52.08)	4.38 (4.17)	20.28 (20.30)
1h	70	260 (H_2O)	$C_{10}H_9N_3O_5$	47.82 (47.85)	3.61 (3.61)	16.73 (16.85)
1i	70	202 (H_2O)	$C_9H_8N_2OCl_2$	46.78 (46.75)	3.49 (3.46)	12.12 (12.24)
1j	40	176 (H_2O)	$C_7H_8N_2OS$	49.98 (49.72)	4.79 (4.71)	16.65 (16.14)
1k	85	154 (iPrOH)	$C_7H_8N_2OS$	49.98 (50.15)	4.79 (4.83)	16.65 (16.71)

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