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DECARBOXYLATION OF PYROGLUTAMIC ACIDS WITH P_2O_5/CH_3SO_3H : A GENERAL SYNTHESIS OF 5-ARYL-2-PYRROLIDINONES.

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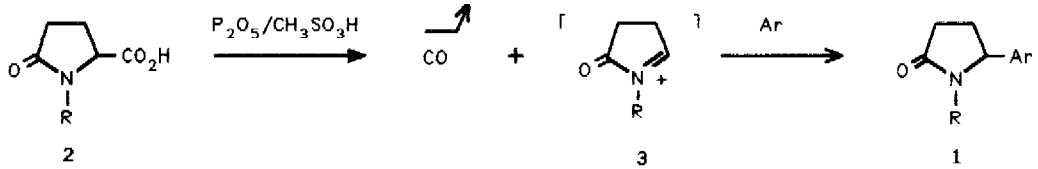
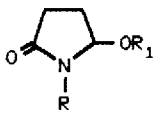
Abstract : Treatment of pyroglutamic acids with acyl-activating reagents (P_2O_5/CH_3SO_3H, PPE ...), possibly in the presence of triethylamine, yields acyl iminium salts, that can react in-situ with aromatic compounds to give the corresponding 5-aryl-2-pyrrolidinones with good yields.

5-Aryl-2-pyrrolidinones **1** are important products because of the potential for a number of these compounds to act as psychotropes.[1] Notwithstanding the many syntheses of **1** reported so far,[2,3] there is still a need for a simple preparation. We now describe an easy route to **1** that demonstrates the potential of the inexpensive, natural compound, pyroglutamic acid (**2** R = H) as an interesting starting material in heterocyclic synthesis.[4]

The acyl iminium salts **3** are the key intermediates in some of these syntheses.[3] We observed that they could be created directly from the pyroglutamic acids **2**,[5] without using 5-hydroxy or 5-methoxy-2-pyrrolidinones (**4**)[6] : by heating acids **2** in a melt with the P_2O_5/CH_3SO_3H mixture,[7] carbon monoxide evolved, as observed for the obtention of iminium salts from aminoacids and acyl-activating reagents.[8-9]The newly created acyl iminium salts **3** then condensed with aromatic compounds, if present, yielding the 5-aryl-2-pyrrolidinones (**1**) in an one-step reaction.



2 **3** **1**



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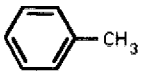
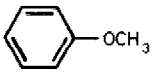
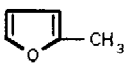
The carbon monoxide evolution began at 60°C with the P_2O_5/CH_3SO_3H mixture; other activating reagents like PPA,[10] PPE[11] or PPSE[12] promoted this reaction too, but with PPA, a higher temperature has to be used, and with PPE and PPSE, it proved to be difficult to isolate a pure product. The decomposition of acid sensitive aromatic compounds (thiophene, 2-methylfuran) can be avoided by the addition of triethylamine or by using a chloroform solution of PPE. No reaction was observed with basic heterocycles like

TABLE 1

Reaction of pyroglutamic acids with aromatic compounds

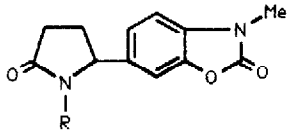
	R	ArH	Reaction conditions			Isolated	bp (°C) (mm Hg)
			t (mn)	T (°C)	method [a]	yield (%) [b]	mp (°C) (solvent)
1	H		60	100	A	28	107 (ether/EtOH)
2	Me	//	60	100	A	27	105 (0.3)
3	H		30	100	A	68	121 (ether/EtOH) [d]
4	Me	//	30	100	A	76	95 (0.2)
5	H		30	100	A	77	145 (0.2) [e] 125 (H_2O) [e]
6	Me	//	30	100	A	90	118 (0.2)
7	H			65	A	0 [c]	
8	//	//	60	100	B	41	140 (0.3) 115 (ether/EtOH)
9	//	//	90	65	C	47	//
10	Me	//		65	A	0 [c]	
11	//	//	60	100	B	31	100 (1.15)
12	//	//	60	65	C	28	//
13	H			65	A	0 [c]	
14	//	//	30	65	B	0	
15	//	//	120	65	C	30	125 (0.3) 81 (ether/EtOH)
16	Me	//		65	A	0 [c]	
17	//	//	30	65	B	0	
18	//	//	120	65	C	40	120 (0.3)

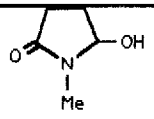
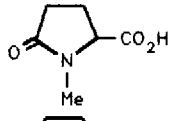
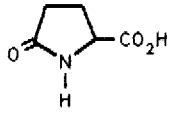
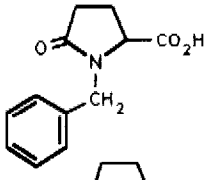
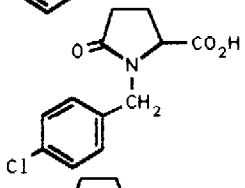
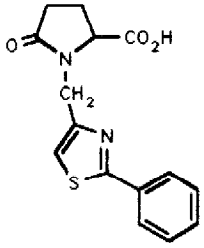
[a] Method A : Pyroglutamic acid (1g), was added to $P_2O_5/MeSO_3H$ (7g, 1/10, w/w) and ArH (1,1eq.); method B : the acyl-activating reagent was $P_2O_5/MeSO_3H$ (7g, 1/10, w/w) and Et_3N 4g ; method C: the acyl-activating reagent was PPE (7g) in $CHCl_3$ (7g). [b] Identification and purity of products were checked by NMR, MS, microanalysis (± 0.4%) and by HPLC (5C-18, MeCN/MeOH 90/10); proportions of detected isomers in the crude were (o/m/p) : entry 3 : 18/13/69%, entry 4 : 13/5/82%, entry 5 : 43/0/57%, entry 6 : 34/0/66%. Only one compound was found in the other cases. [c] Decomposition of the aromatic. [d] Lit. mp : 116-8° C.[13] [e] Lit. mp : 127) C.

2-methylbenzimidazole or indole, or with deactivated aromatic products such as chlorobenzene. Addition of sulfuric acid or aluminium trichloride to the activating reagent inhibit the reaction also.[9] As shown in Tables 1 and 2, the reaction is quite general, providing medium to good yields, and is not influenced by the nitrogen substituent of the pyroglutamic acid. Another important fact shown in Table 2 (entries 1 and 2), is that it can be more interesting to use a pyroglutamic acid than the corresponding 5-hydroxy-2-pyrrolidinone.

Table 2

Reaction of pyroglutamic derivatives with N-methyl benzoxazolone



	Pyroglutamic derivative	Reaction Conditions[a]		Isolated yield (%)	mp (solvent)
		t (mn)	T (°C)		
1		90	140	18	166 (EtOH)
2		90	140	71	166 (EtOH)
3		90	130	82	207 (H_2O)
4		90	120	39	117 (EtOH)
5		120	140	55	160 (MeOH)
6		60	120	47	111 (H_2O/EtOH)

[a] Pyroglutamic derivative : 1g, N-methyl benzoxazolone : 1 eq., P_2O_5/CH_3SO_3H 1/10 : 7g

In a typical procedure, a well stirred mixture of pyroglutamic acid 5g (39 mmole), N-methyl benzoxazolone 6g (40 mmole) and P_2O_5/CH_3SO_3H 1/10,[7] 35g, was heated at 130° for 1 hour. The carbon monoxide evolution was abundant during the first 30 mn. After cooling, the solution was added to water (200 ml), then extracted with dichloromethane and dried (Na_2SO_4). After evaporation, the solid was recristallized from water, yield 82%; mp. 166°, IR (nujol) ν cm^{-1}: 1675, 1770; ^1H NMR (dmso d_6) δ ppm : 2-2.8 (m, 4H), 3.34 (s, 3H), 4.5-4.8 (m, 1H), 7.15-7.22 (m, 3H), 8.05 (s, 1H);[14] Correct C, H, N analysis.

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(1) UCB, S.A., Ger.Offen. 2,136,571 (1972); *Chem. Abstr.*,**76**, 113055y (1972). D. Lednicker and L. A. Mitscher, "The Organic Chemistry of Drug Synthesis" vol. 1 p. 235, Wiley and Sons, Inc., New York, N.Y.(1977). V. Bocchi, G. P. Gardini and M. Pinza, *Farmaco, Ed. Sci.*, ***26***, 429 (1971).

(2) W. G. Frankenburg and A. A. Vaitchums, *J. Am. Chem. Soc.*,***79***, 149 (1957). V. Bocchi and G.P. Gardini, *Org. Prep. Proced.*, **1**, 271 (1969). Japan Tobacco and Salt Public. Corp. Jap. P. 80 31,005 (1980); *Chem. Abstr.*,**93**, 186151y (1980). T. Nagazaka, M Abe, N. Ozawa, Y. Kozuki and F. Hamaguchi, *Heterocycles*, **20**, 985 (1983). M. Malmberg and K. Nyberg, *Acta Chem. Scand., Ser. B*, **B33**, 69 (1979).

(3) V. Bocchi, L. Chierici and G. P. Gardini, *Tetrahedron*, **26**, 4073 (1970).

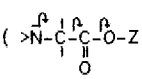
(4) Pyroglutamic acid is an inexpensive chemical sold in bulk by UCIB, 27540 Yvry La Bataille, France.

(5) N. Kolocouris, *Bull. Soc. Chim. France*, **3**, 1053 (1973). N. Kolocouris and B. Rigo, *Chim. Chron., New Series*, **11**, 309 (1982).

(6) Electrochemical decarboxylation of pyroglutamic acids in water or methanol yields compounds **4** : T. Iwasaki, H. Horkawa, K. Matsumoto and M. Miyoshi, *J. Org. Chem.*, **44**, 1552 (1979).

(7) P. E. Eaton, G. R. Carlson and J. T. Lee, *ibid.*,**38**, 4071, (1973).

(8) V. I. Mahsimov, *Tetrahedron*, **21**, 687 (1965). H. Rapoport, *Lect. Heterocyclic Chem.*, **IV**, S-47 (1978).

(9) We thought the mechanism of this decarboxylation to be the same as for the amino-acids ()[8] (carbon monoxide was detected with a Dräger tube).The failure of the reaction in the presence of H_2SO_4 or $AlCl_3$ supports too this mechanism.

(10) L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, p.894, John Wiley and Sons, Inc.,(1967).

(11) ibid., p.893

(12) T. Imamoto, H. Yokoyama and M. Yokoyama, *Tetrahedron Lett.*, **22**, 1803, (1981). K. Yamamoto and H. Watanabe, *Chem. Lett.*, 1225 (1982).

(13) K. W. Rosenmund and P. Engels, *Arch. Pharm.*, **284**, 16, (1951).

(14) This peak disappears upon addition of deuterium oxide.

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