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Synthesis of Novel Imidazolidinones

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Summary. The preparation of a number of new imidazolidinones by a simple method based on the reaction of α-aminocarboxamides with carbonyl compounds is described.

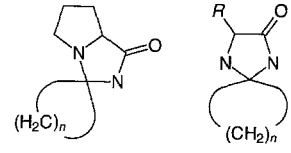
Keywords. α-Aminocarboxamides; Imidazolidinones; Spiroimidazolidinones; Carbonyl compounds.

Synthese neuer Imidazolidinone

Zusammenfassung. Die Darstellung einer Reihe neuer Imidazolidinone durch Reaktion von α-Aminocarboxamiden mit Carbonylverbindungen wird beschrieben.

Introduction

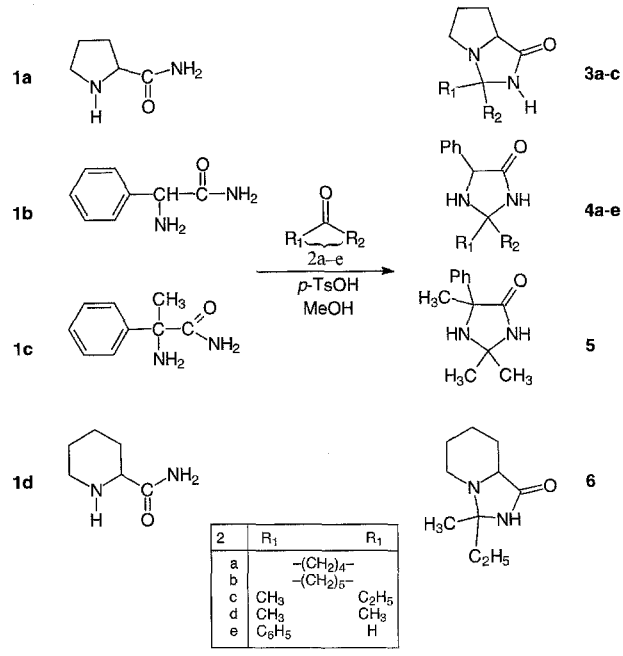
In the course of our investigations on structure-activity relationships of antiepileptic agents, the synthesis of novel Pyrrolo[1, 2-*c*] imidazol-l-ones(**3**) appeared to be of interest. To our knowledge, the structurally closest compounds with respect to **3** reported in the literature are spiroimidazolidinones (**4**) which have been prepared by the reaction of α-aminonitrilies with carbonyl compounds in the presence of sodium alkoxides [1, 2] or by the reaction of O-carbobenzoxyaminoacid amides with carbonyl compounds followed by removal of the carbobenzoxy group by catalytic hydrogenation [3] (Scheme 1).



3a: $n = 4$ **3b**: $n = 5$ **4**

Scheme 1

Searching for a simple and general method for the preparation of Pyrrolo[1, 2-*c*] imidazol-l-ones (**3a, b**), experimental condition for the reaction of prolinamide (**1a**) with carbonyl compounds (**2a, b**) were investigated. In this paper we report the general applicability of the above method, allowing the preparation of a number of hitherto unknown imidazolidinones.



2	R_1	R_1
a	$-(CH_2)_4-$	
b	$-(CH_2)_5-$	
c	CH_3	C_2H_5
d	CH_3	CH_3
e	C_6H_5	H

Scheme 2

Results and Discussions

Preliminary experiments involving the reaction of α-aminocarboxamides **1a**, with carbonyl compounds **2a**, **b**, in refluxing benzene or toluene without the use of a catalyst or in the presence of *p*-toluenesulfonic acid as well as in refluxing methanol were unsuccessful. However, good yields of imidazolidinones were obtained when the same reactions were carried out in refluxing methanol in the presence of p-toluenesulfonic acid as catalyst (Scheme 2, Table 1). With the exception of **4d** which has previously been prepared by another method [2], all imidazolidinones prepared in the present study are hitherto unreported.

In conclusion, the present method has the advantage of easily available starting materials, mild reaction conditions, and simple work up procedures. The main limitation of the method is that relatively bulky ketones such as naphthoquinone failed to give any detectable product. The biological activities of **3a**, **b** are currently under investigation.

Experimental

Melting points were determined with a Reichert hot plate melting point apparatus and are uncorrected. TLC analyses were performed on 250-Eastman 13181 silica gel sheets; spots were visualized under ordinary fluorescent light or 254 nm UV light. Mass spectra were recorded with a Finnigan TSQ-70 instrument. ^{1}H NMR spectra were measured in deuterochloroform with a Bruker AC-80 (80 MHz) spectrometer relative to TMS as internal standard. Infrared spectra were recorded on a Perkin-Elmer 781 spectrometer. α-Aminocarboxamides **1a–d** were prepared according to reported methods [4–7].

Table 1

	Yield %	m.p. (°C)	IR (KBr) $\nu(cm^{-1})$	^1H NMR ($CDCl_3$) δ(ppm)	MS (70 eV) m/t (M^+)
3a	53	98 – 100	2980, 1700, 1440	1.61 (m, 12H), 2.7 (m, 2H), 3.87 (t, 1H, J = 9Hz), 6.9 (br, 1H, NH)	180
3b	70	157 – 158	1440, 2940, 1700	1.7 (m, 14H), 2.8 (m, 2H), 3.91 (t, 1H, J = 8Hz), 7.88 (br, 1H, NH)	194
3c	40	93 – 95	1700, 1450	0.94 (t, 3H, J = 9Hz), 1.38 (s, 3H), 1.7 (m, 6H), 2.86 (q, 2H), 3.93 (t, 1H), 6.6 (br, 1H, NH)	168
4a	86	157 – 158	1705, 1450, 1340	1.79 (s, 8H), 2.47 (br, 1H), 7.32 (m, 5H), 7.6 (br, 1H, NH)	216
4b	72	181	2960, 1705, 1460	1.67 (m, 10H), 2.14 (br, 1H, NH), 4.69 (s, 1H), 7.49 (m, 5H), 7.71 (br, 1H, NH)	230
4c	65	108	1350, 1450, 1700	0.98 (t, 3H, J = 9Hz), 1.45 (s, 3H), 1.57 (q, 2H, J = 9Hz), 2 (br, 1H, NH), 4.67 (s, 1H, J = 5Hz), 7.38 (m, 5H), 7.6 (br, 1H, NH)	204
4d	75	156 – 157	1715, 1440, 1340	1.49 (s, 6H), 3.2 (br, 1H, NH), 4.72 (s, 1H), 7.37 (m, 5H), 7.9 (br, 1H, NH)	190
4e	63	172 – 173	3160, 1460, 1695	2.2 (br, 1H, NH), 4.7 (s, 1H), 5.67 (s, 1H), 6.8 (br, 1H, NH), 7.43 (m, 10H)	208
5	70	159	1705, 1440,	1.23 (s, 3H), 1.52 (s, 3H), 1.64 (s, 3H), 2.17 (br, 1H, NH), 7.01 (br, 1H, NH), 7.39 (m, 5H)	204
6	40	170	2990, 1700, 1430	0.99 (t, 3H, J = 9Hz), 1.38 (s, 3H), 1.7 (m, 8H), 2.75 (q, 2H), 3.9 (t, 1H), 7.5 (br, 1H, NH)	182

General procedure for the preparation of imidazolidinones **3–6**

A solution of α-aminocarboxamide (**1**, 0.01 mol), carbonyl compound (**2**, 0.03 mol), and *p*-toluenesulfonic acid (0.02 g) in 20 ml MeOH was refluxed with stirring. The reaction was monitored by TLC until complete disappearance of **1** (usually, *ca* 6 hours were required). The solvent was then removed by a rotatory evaporator, the residue was dissolved in chloroform (50 ml), washed successively with sodium hydrogen carbonate solution (25 ml) and water (25 ml), and dried over anhydrous magnesium sulfate. After evaporation of the chloroform, the residue was crystallized from ethyl acetate-hexane (4:1) to give imidazolidinones **3–6** (Table 1).

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