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PYRROLIDINES BY INTRAMOLECULAR ADDITION OF KOLBE RADICALS GENERATED FROM β-ALLYLAMINOALKANOATES

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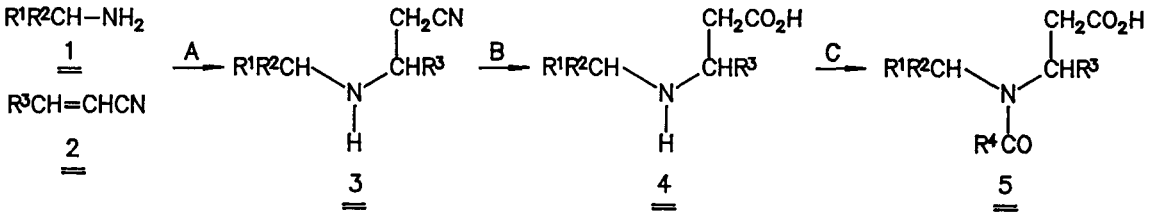
Abstract 3-Alkyl-substituted pyrrolidines 7 are obtained by Kolbe electrolysis of β-allylaminoalkanoates 5, intramolecular addition of the radical and mixed coupling with the radical of a coacid.

Five membered carbocycles[1] and heterocycles[2,3] can be effectively prepared by a 5-exo-trig-cyclization via radicals mostly generated from bromides. We have demonstrated, that radicals produced from carboxylic acids by Kolbe-electrolysis can also be used for this cyclization, as shown in the preparation of substituted tetrahydrofurans[4]. The intramolecular Kolbe-addition has a major advantage compared with the radical chain addition starting from the bromide, that two C-C bonds are being formed, whilst in the latter only one C-C bond and one C-H bond are joined in most cases[5]. Furthermore the second carbon substituent can be varied simply and in a wide range by the choice of the coacid in the mixed Kolbe-electrolysis.

We have now extended this methodology to the synthesis of 3-substituted pyrrolidines by the Kolbe-electrolysis of β-(N-acyl-N-allylamino)- and β-(N-acyl-N-propargylamino)-propionates and -butyrates (5) with different coacids. Acids 5 were prepared by addition of amines 1 to unsaturated nitriles 2, subsequent hydrolysis of the nitriles 3 to acids 4 and acylation of the amino group to 5 (Table 1).

The acids 5 are electrolyzed with different coacids 6 to afford via cyclization of the intermediate 3-aza-5-hexenyl-radical and its coupling with the radical of the coacid 3-substituted pyrrolidines 7 in fair to good yields (Table 2).



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
a	H_2C=CH–	H	H	H	d	–HC=CH–$(CH_2)_2$–		CH_3	H
b	H_2C=CH–	H	CH_3	H	e	H_2C=CH–	H	H	CH_3
c	HC≡C–	H	CH_3	H	f	H_2C=CH–	H	CH_3	CH_3

A: Reflux; B: Reflux with 10 n sulfuric acid: C: Table 1

Table 1: Preparation of β-(N-acyl-N-allylamino)- and β-(N-acyl-N-propargyl-amino)propionates and -butyrates (5)

Educts		Products, Yields (%)[a]		
1	2	3	4	5
a	a	a: 85	a: 97	a: 72[b] e: 83[c]
a	b	b: 75	b: 90	b: 70[b] f: 85[c]
c	b	c: 40	c: 53	c: 60[b]
d	b	d: 57	d: 77	d: 85[d]

a) Structures confirmed by ^{1}H-NMR, MS and elemental analyses. -
b) Reflux with ethyl formiate. - c) Acetic anhydride in H_2O/NaOH. -
d) DCC/formic acid in methylenechloride/pyridine.

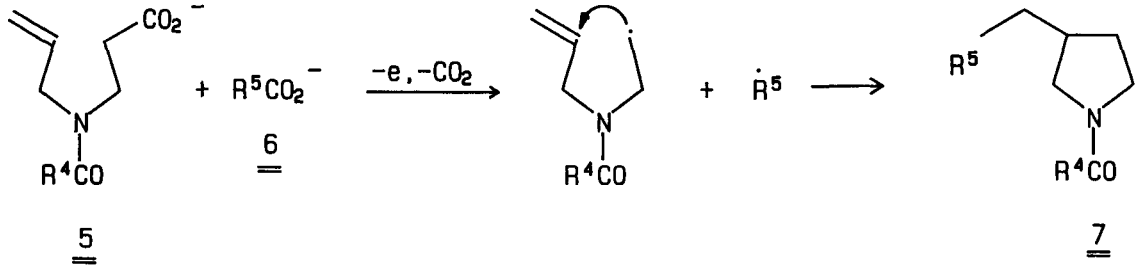
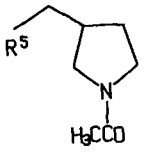
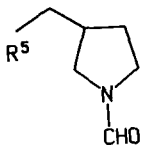
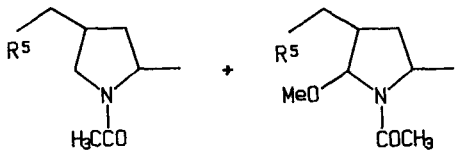
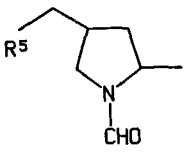
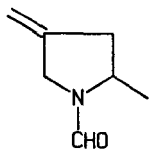
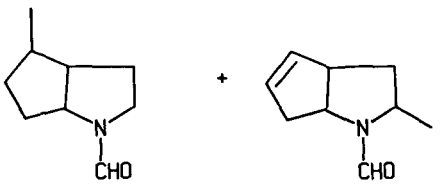


Table 2: Mixed Kolbe electrolysis[a] of β-allylamino- and β-propargylamino propionates 5 with coacids 6 to pyrrolidines 7

Nr.	Acid	Coacid 6 R^5	Pyrrolidine 7	Yield (%)[b]
1	5e	CH_3		58
		C_5H_{11}		46
		$CH_3O_2C(CH_2)_4$		53
2	5a	CH_3		58
		C_5H_{11}		45
3	5f	CH_3		56[c]
4	5b	CH_3		67
		C_5H_{11}		63
5	5c	CH_3		45
6	5d	CH_3		60[d]

a) 4 eq. R^5CO_2H, 5% neutralization, T = 40-45° C, 1.3 - 1.5 eq. current, methanol, platinum electrode, undivided cell.- b) All structures confirmed by ^1H-NMR, MS and elemental analysis.- c) Product ratio 4:1.- d) Product ratio 2:1. -

Formylation protects the amino group from further oxidation under the conditions of the Kolbe electrolysis. The acetyl group is less desactivating[6], which leads to a concurrent α-methoxylation[7] (Nr. 3). The vinyl radical generated from 5c is apparently much more reactive than the methylene radical[8], so that hydrogen abstraction, probably from the solvent methanol, becomes the dominant reaction and coupling with the R^5-radical is suppressed (Nr. 5). Steric hindrance[9] in the secondary radical produced from 5d leads to some disproportionation (Nr. 6).

Despite these minor limitations the method offers an alternative entry to pyrrolidines[10] via simultaneous formation of the C3-C4 bond and introduction of a 3-substituent. In most of the other radical cyclizations to pyrrolidines the C2-C3 bond is closed via α-acylamino radicals[3].

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