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A DECARBOXYLATIVE CARBON-CARBON FORMATION REACTION

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The preparation of ylids via abstraction of a proton from an onium salt has been employed almost to the exclusion of other routes. An attractive alternative which has received little attention in the literature involves the decarboxylation of an appropriate betaine (1). We wish to report a convenient general synthesis of 1-(2-hydroxy-2-arylethyl)pyridinium halides which most likely proceeds by such a mechanism.

The action of bromoacetic acid and pyridine (Py) in the presence of benzaldehyde at 120° has been found to give 1-(2-hydroxy-2-phenylethyl)pyridinium bromide (1) in 75% yield.

$$2\ Py + BrCH_2CO_2H + \text{ØCHO} \xrightarrow[\text{ØNO}_2]{\Delta} \underset{1}{[Py^+-CH_2-CH(OH)-\text{Ø}]\ Br^-}$$

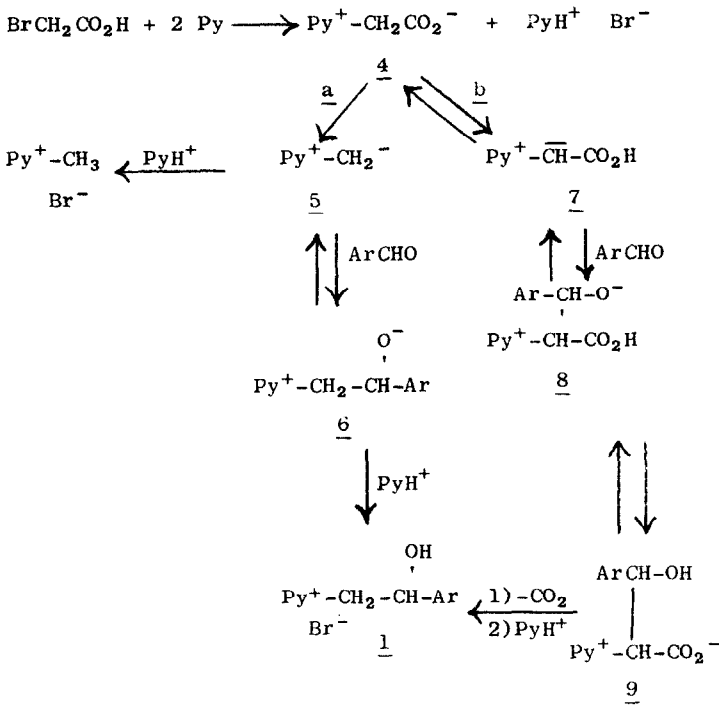
The solvent may be excess aldehyde, nitrobenzene or dimethylformamide. As can be seen in Table I, the reaction is fairly general; electron donating or withdrawing groups may be placed on the pyridine or aldehyde. Bromoacetic acid may be replaced by chloroacetic acid, ethyl bromoacetate or other substituted α-bromoacetic acids such as α-bromopropionic or α-bromobutyric acid.

Some information pertaining to the mechanism of these reactions has been obtained. The two possible pathways which may be involved are illustrated in Chart I. Pathway a involves decarboxylation of the initial adduct to an ylid followed by condensation. Pathway b is essentially the reverse sequence; the condensation proceeds prior to decarboxylation. The formation of a side product, the N-methylated salt of the starting pyridine, can only result from ylid 5. Therefore pathway b requires that 5 also be formed concurrently with 7 and that 5 is completely protonated.

Evidence for the initial adduct formation was obtained when the conjugate acid of 4 was obtained from a mixture of bromoacetic acid and pyridine in bromobenzene. Treatment of this substance with pyridine and benzaldehyde gave the expected adduct 1 in 72% yield.

Chart I

Mechanistic Possibilities for Reaction of Bromoacetic Acid, Pyridine and Benzaldehyde.



As depicted in Table II, increasing amounts of aldehyde gave more adduct (1) at the expense of the N-methylated pyridine. More electrophilic aldehydes favor the adduct over the N-methylated pyridine. A 4-cyano group which stabilizes the pyridinium ylid decreases the ratio of condensation to protonation (23/77) relative to the ratio for the unsubstituted ylid (96/4) even though the aldehyde concentration is increased. Although other explanations are possible, a simple competition between a proton and an aldehyde molecule for ylid 5 seems most reasonable.

Table I

1-(2-Hydroxy-2-arylethyl)pyridinium Bromides[a]

$[YC_5H_4N^+-CH_2-CH(OH)R]\ Br^-$

Y	R	Yield (%)	Mp(°C)	Lit.[b] mp(°C)
H	phenyl	75	237-239	230.5
H	p-tolyl	58	207-209	212.5
H	trichloromethyl	20	220-221	220-222
H	2-furanyl	51	189-192	215
4-cyano	phenyl	69	234-235	---
3-methyl	phenyl	50	163-165	---
4-methyl	phenyl	29	172-175	---
H	3,4-methylenedi-oxyphenyl	59	232-234	147
H	4-methoxyphenyl	16	---	180-181
H	4-nitrophenyl	80	275-276	270-272
4-cyano	4-nitrophenyl	14	256-257	---
4-cyano	p-tolyl	64	228-229	---
4-methyl	3,4-dichlorophenyl	61	189-192	---
4-methyl	3,4-methylenedi-oxyphenyl	72	261-262	---

[a]The NMR spectra of all the adducts are in complete accord with the proposed structure. Satisfactory analysis were also obtained for all the adducts except when Y=H and R=4-methoxyphenyl. Here the adduct could not easily be separated from the N-methylated pyridine. The NMR spectrum of this mixture was consistent.

[b]F. Krohnke, Chem. Ber., 67 656 (1934).

Table II

Product Distribution. Reaction of Bromoacetic Acid and Substituted Pyridines with Various Aromatic Aldehydes[a]

Y[b]	X[c]	Moles Aldehyde/ Moles Bromo-acetic Acid	% Adduct	% N-Methyl-ated Pyri-dine	Total Yield (%)
H	H	10[d]	100	0	75
H	H	4	97	3	75
H	H	3	94	6	77
H	H	2	90	10	77
H	H	1	65	35	93
H	4-OCH_3	1	31	69	80
H	4-NO_2	1	96	4	82
4-CN	4-NO_2	2.5	23	77	99

[a]The product distribution was determined by integration of the appropriate peaks in the NMR spectra of the crude products. Controls indicated that the products were stable under the reaction conditions.

[b]Pyridine substituent.

[c]Aldehyde substituent

[d]The solvent here was excess aldehyde. In all other cases cited, the solvent was nitrobenzene.

Evidence favoring pathway a was obtained when aliquots were taken from a heated mixture of N-carboxymethylpyridinium bromide, pyridine and benzaldehyde. The NMR spectrum of these aliquots indicated only starting material and 1 were present. No evidence was found for the presence of a structure corresponding to 8 or 9. One can only conclude that pathway b is not operative or that 8 and 9 decompose much faster than they form.

While the evidence is not conclusive, we believe the evidence favors pathway a over pathway b.

REFERENCES

1. (a) R. K. Howe and K. W. Ratts, Tetrahedron Letters 27, 4743 (1967); (b) M. R. F. Ashworth, R. P. Daffern and D. Ll. Hammick, J. Chem. Soc., 809 (1939); (c) P. Haake and J. Mantecón, J. Am. Chem. Soc., 86, 5230 (1964).