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N-VINYL-2-ETHOXYPYRROLIDINIMINIUM TETRAFLUOBORATE: AN UNUSUALLY REACTIVE IMIDATE SALT

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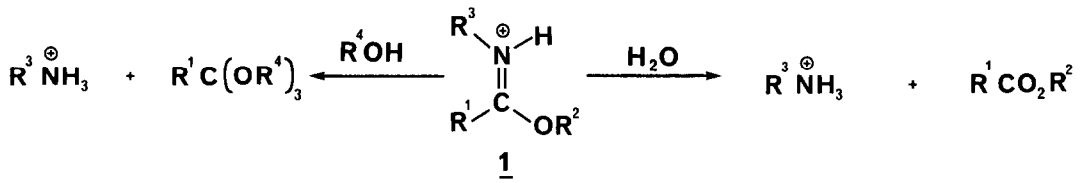
Abstract: N-Vinyl-2-ethoxypyrrolidiniminium tetrafluoborate, 3, constitutes a new class of imidate salt which reacts with water, under neutral conditions, to give acetaldehyde and ethyl 4-aminobutyrate but with alcohols to give the N-(1-alkoxy-1-ethyl)-2-alkoxy imidate, 9 or 10.

Our search for a new synthon, convertible to indolizidine alkaloids[1], has led to the preparation of the first member of a novel class of imidate salts, N-vinyl-2-ethoxypyrrolidiniminium tetrafluoborate, 3. Simple imidate salts such as 1 are easily prepared and have been known for many years.[2] One of the interesting reactions exhibited by 1 is facile hydrolysis or alcoholysis leading to the corresponding ammonium salt, ester or ortho-ester, respectively.[2] We have observed that imidate 3 is unique in its reactivity towards water, affording amino-ester 4 but only after loss of the vinyl group as acetaldehyde. Imidate 3 also gives unusual reactions with alcohols leading to N-(1-alkoxy-1-ethyl)-2-alkoxy iminium salts such as 9 or 10.



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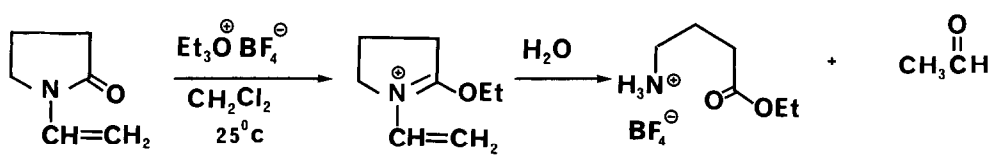
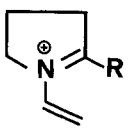
Seeman has reported the preparation of N-vinyl-2-alkylpyrrolidiniminium perchlorate, 5(R = alkyl), from N-vinyl-2-pyrrolidinone, 2, and alkyllithium reagents after quenching with perchloric acid.[3] Although 5 is structurally similar to 3, 5 is unusually stable to hydrolysis, requiring aqueous acid to achieve loss of the vinyl group, and giving 2-alkyldihydropyrrole derivatives rather than ring opening. The presence of the 2-ethoxy group in 3 imparts greatly enhanced reactivity with water and alcohols, relative to 5, and for this reason 3 should be considered a new class of imidate.



2 3 4

Imidate salt 3 was prepared by reaction of N-vinyl-2-pyrrolidinone, 2, with triethyloxonium tetrafluoborate[4] (CH_2Cl_2, 25°C), analogous to the preparation of other imidate salts, 1[5], and was isolated in quantitative yield as a colorless, crystalline solid.[6] We observed that upon exposure to the atmosphere, the vinyl protons of 3 (by nmr) slowly disappeared. We attributed this to the hygroscopic nature of the imidate and subsequent reaction of 3 with one-hundred equivalents of water (neat, 25°C) afforded ethyl 4-aminobutyrate[7], in 85% yield, as the tetrafluoborate salt, 4. We found that treatment of the water which had been removed from 4 ('in vacuuo', 25°C) with 2,4-dinitrophenylhydrazine in ethanol gave crystals of the 2,4-dinitrophenylhydrazone derivative of acetaldehyde. Clearly, the elements of water, under neutral conditions, had added across the vinyl group with its subsequent loss as the aldehyde. This contrasts with the observation by Seeman that loss of the vinyl group in 5 required aqueous acid.[3] Schmir and others[8] have proposed a mechanism for the hydrolysis and alcoholysis of 1 involving initial attack of water or alcohol on the C-2 position of the iminium salt followed by proton transfer to the nitrogen. If one assumes such an addition of water to 3, but with proton transfer to the carbon of the vinyl group, a new imidate, 6, would be the product. Imidate 6 is susceptible to attack by a second equivalent of water, completing hydration of the vinyl group to give 7. Acetaldehyde would result from C-N bond cleavage in 7 with subsequent fission of the ring leading to 4.



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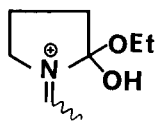

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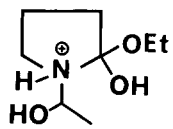

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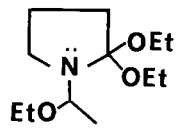

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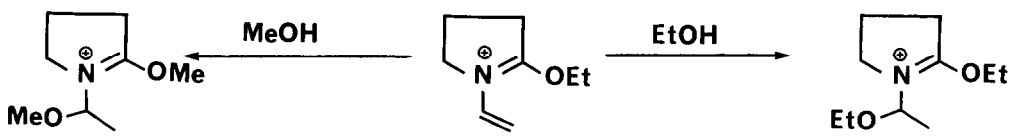
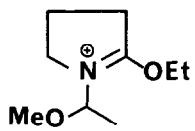
Imidate 1 also reacts with alcohols to give the ammonium salt and the ortho-ester, but this reaction is known to be slow.[2,9] Once again, we have observed a unique product upon reaction of 3 with alcohols. Rather than loss of the vinyl group and ring opening as observed upon reaction with water, reaction of 3 with one-hundred equivalents of ethanol (neat, 25°C) gave N-(1-ethoxy-1-ethyl)-2-ethoxypyrrolidiniminium tetrafluoborate, 9[6], in 86% yield. By analogy with imidate 1, one might have expected the ortho-ester analog of 3, lactam acetal 8



10 3 9

as the product. Although 8 may be an intermediate in the formation of 9, we were unable to observe 8 in reactions of 3 for up to 48 hours, even with large excesses of ethanol (2, 5, 100 or 500 equivalents). It is not clear if this phenomenom is due to the lability of 8 or to a different mechanistic pathway.

To further probe the possibility of lactam acetal formation as an intermediate in the reactions with alcohol, we allowed 3 to react with one-hundred equivalents of methanol. We observed what appeared to be an equilibrium mixture of N-(1-methoxy-1-ethyl)-2-methoxypyrrolidiniminium tetrafluoborate, 10[6], and N-(1-methoxy-1-ethyl)-2-ethoxypyrrolidiniminium tetrafluoborate, 11, in 82% yield in an 8:2 ratio, respectively. This mixture was established within thirty minutes with complete loss of the vinyl group of 3(by nmr) and was not significantly



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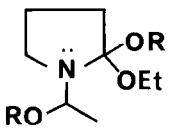

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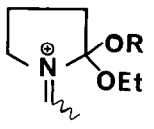

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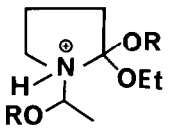

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different after twenty four hours. After forty eight hours, however, 10 was isolated as the only product. Reaction with up to five-hundred equivalents of methanol had no apparent affect on the rate of this conversion but reaction with two or five equivalents gave the same 8:2 mixture within thirty minutes but gave significantly slower conversion to 10. Once again, we were unable to observe lactam acetal intermediates such as 12, isolating only 10:11 as a mixture, or, 10 in pure form after forty eight hours. We were unable to isolate 11 and its presence was inferred by the complete loss of the vinyl protons in 3(by nmr), the appearance and then slow disappearance of ethoxy protons at 4.44 ppm(q, 2H, J = 3.2 Hz) and 1.35 ppm(t, 3H, J = 3.2 Hz).

Products such as 9, 10 and 11 can be explained by initial addition of alcohol to the imine bond of 3, as observed with water, followed by proton transfer to the vinyl group. This would result in species such as 13 as a reactive intermediate. Although addition of a second equivalent of alcohol would give the lactam acetal, only the imidate salt 9, 10 or 11 was observed. Protonation of the nitrogen, via proton transfer after the addition of the second equivalent of alcohol, would give the protonated lactam acetal 14 and could explain the very slow loss of ethoxy to give 10. This is speculative at this point since we have not observed or isolated species such as 14. It should be noted that other N-alkylated lactam acetals have been isolated and characterized under conditions more vigorous than those employed herein[10], suggesting reasonable stability for species such as 8 or 12. The lack of evidence for lactam acetal formation in the reaction of 3 with alcohols is therefore unusual.

The N-vinyl-2-alkoxy imidate salt, 3, constitutes a unique class of imidates which react with water under neutral conditions, faster than the comparable imidate salt 5, and without the requirement of acid. The products are the result of an unusual proton transfer to the vinyl group. If one compares intermediate 7 with 14, it appears that loss of the hydroxyl proton from 7 is necessary for C-N bond cleavage with loss of aldehyde, impossible with 14. The formation of acetaldehyde raises the interesting possibility of 3 being used as an aldehyde synthon. The N-vinyl lactam progener of 3 is easily prepared by treatment of the simple lactam with the appropriate alkyne and base[11]. Since reaction of 3 with water leads to loss of the vinyl group as acetaldehyde, we have effected the transformation: acetylene ⟶ acetaldehyde. Further work

is required to establish this as a general method, however. The final product of hydrolysis results from ring opening to the amino-ester 4. Cleavage of imidate salts to ammonium salts and esters has precedent but the reactivity of 3 is comparable to that of simple analogs such as 1 rather than the more highly substituted analogs which tend to resist hydrolysis. Addition of alcohol across the vinyl group of 3 is facile and isolation of the imidate salt, 9, 10 or 11, rather than the lactam acetal is unusual. It is clear that the unique structure of 3 leads to several variations in the normal reactivity of simple imidate salts which are interesting and potentially useful.

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6. Spectral data for selected compounds: 3: m.p., 102.0-102.5°C; IR(KBr): 520, 870, 912, 1040, 1245, 1320, 1392, 1457, 1490, 1615 and 2970 cm^{-1}; ^1H nmr($CDCl_3$, TMS):δ6.40-6.98(1H, dd, J = 4.0, 8.0 Hz, +NCH=CH_2), 4.82-5.24(2H, m, +NCH=CH_2), 4.52(2H, q, J = 3.4 Hz, -OCH_2CH_3), 3.90 (2H, t, +N$CH_2CH_2CH_2$-), 3.25(2H, t, +N=C-CH_2CH_2-), 2.08-2.62(2H, m, +N-$CH_2CH_2CH_2$-) and 1.48 ppm(3H, t, J = 3.4 Hz, -OCH_2CH_3). 9: m.p.. 66.5-67.0°C; IR(KBr): 525, 635, 875, 930, 948, 1060, 1180, 1235, 1320, 1395, 1422, 1510, 1660 and 3000 cm^{-1}; ^1H nmr($CDCl_3$, TMS):δ5.15(1H, q, 3.0 Hz, +NCH(OEt)Me), 4.48(2H, q, J = 3.2 Hz, +N=C-OCH_2CH_3), 3.0-3.92(6H, m), 2.02-2.55(2H, m, +N-$CH_2CH_2CH_2$-), 1.45(3H, t, J = 3.2 Hz, +N=C-OCH_2CH_3), 1.28(3H, t, J = 3.0 Hz, +NCH(OEt)CH_3) and 1.12 ppm(3H, t, J = 3.4 Hz, +NCH(CH_3)-OCH_2CH_3). 10: m.p., 151.5-152.0°C(d); IR(KBr): 520, 535, 631, 845, 930, 943, 1060, 1280, 1380, 1410, 1670 and 2930 cm^{-1}; ^1H nmr(d_6DMSO, TMS): δ5.09(1H, q, J = 3.0 Hz, +NCH(OMe)Me), 4.11(3H, s, +N=C-OCH_3), 3.40-3.85(2H, bd t, +NCH_2CH_2-), 3.17(3H, s, +NCH(Me)-OCH_3), 2.88-3.40(2H, m, +N=C-CH_2-), 1.82-2.46(2H, m, +N-$CH_2CH_2CH_2$-) and 1.27 ppm(3H, t, J = 3.0 Hz, +N-CH(OMe)CH_3).
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