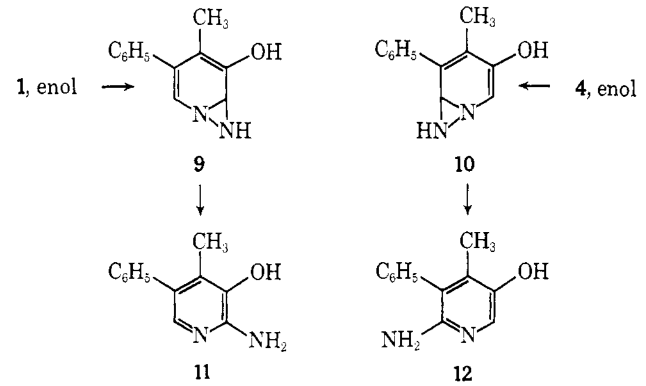

tautomeric 1,7-diazabicyclo[4.1.0]heptadienol **10**. It was previously suggested that the pyridine mixture observed in the reaction of the 2,3-dihydro tautomer **1** arose by cleavage of the diazepine ring and recyclization of an acyclic intermediate to **11** and **12**.[3,4] In view of the interconvertibility of **1** and **4** and the findings with the 1,5-dihydro compound, however, it is possible that the formation of **11** and **12** from the 2,3-dihydro isomer does not involve a common precursor and that the 2-aminopyridine is generated from the bicyclic valence tautomer **9**.

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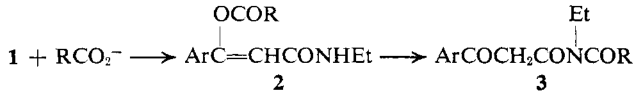
Stable Enol Esters from N-*t*-Butyl-5-methylisoxazolium Perchlorate

Sir:

We wish to report that the intramolecular O,N-acyl migration of enol esters derived from isoxazolium salts can be prevented by the bulky N-*t*-butyl substituent.

The acyl migration rearrangement is a possible side reaction in the synthesis of peptides using N-ethyl-5-phenylisoxazolium-3′-sulfonate (**1**). Although high yields are obtained in peptide syntheses with **1** under optimum conditions, lower yields result if the addition of the amine component to the solution of the enol ester **2** is delayed.[1] Slow rearrangement, which has been observed in studies of model unsulfonated enol esters,[2] presumably gives the less useful acylating agent **3** under these conditions.[1] Therefore, isoxazolium salts which give stable enol esters are of special interest because they might be still more efficient than **1** in peptide synthesis and would allow isolation, rigorous purification, and storage of the intermediate acylating agents.

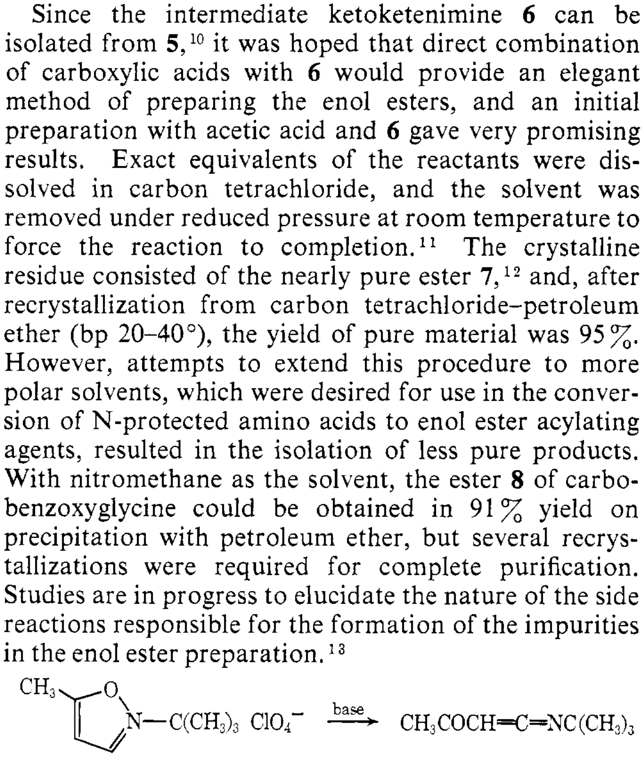


$$1 + RCO_2^- \longrightarrow Ar\overset{OCOR}{\overset{|}{C}}=CHCONHEt \longrightarrow ArCOCH_2CO\overset{Et}{\overset{|}{N}}COR$$

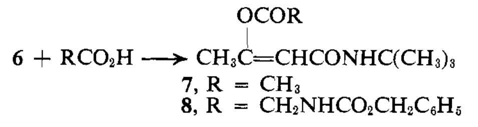
2 3

One approach[3] to the design of improved isoxazolium salt peptide reagents was suggested by the superiority of **1** compared to the N-methylisoxazolium zwitterion in test preparations, which indicated that the esters from **1** were less susceptible to rearrangement, owing to the increased bulk of the N-ethyl group.[1] Enol esters with still bulkier N-alkyl substituents would then be expected to be even more resistant to the side reaction.[7] A test of the simple steric approach was made possible by the discovery of a convenient method for the *t*-butylation of isoxazoles.[9] Our preliminary investigation has revealed that the enol esters from the new reagent N-*t*-butyl-5-methylisoxazolium perchlorate (**5**)[10] are stable compounds which have synthetic utility as acylating agents.

Since the intermediate ketoketenimine **6** can be isolated from **5**,[10] it was hoped that direct combination of carboxylic acids with **6** would provide an elegant method of preparing the enol esters, and an initial preparation with acetic acid and **6** gave very promising results. Exact equivalents of the reactants were dissolved in carbon tetrachloride, and the solvent was removed under reduced pressure at room temperature to force the reaction to completion.[11] The crystalline residue consisted of the nearly pure ester **7**,[12] and, after recrystallization from carbon tetrachloride–petroleum ether (bp 20–40°), the yield of pure material was 95%. However, attempts to extend this procedure to more polar solvents, which were desired for use in the conversion of N-protected amino acids to enol ester acylating agents, resulted in the isolation of less pure products. With nitromethane as the solvent, the ester **8** of carbobenzoxyglycine could be obtained in 91% yield on precipitation with petroleum ether, but several recrystallizations were required for complete purification. Studies are in progress to elucidate the nature of the side reactions responsible for the formation of the impurities in the enol ester preparation.[13]



5 6



$$6 + RCO_2H \longrightarrow CH_3\overset{OCOR}{\overset{|}{C}}=CHCONHC(CH_3)_3$$

7, R = CH_3
8, R = $CH_2NHCO_2CH_2C_6H_5$

The enol esters are sufficiently stable for storage and use as synthetic intermediates. In contrast to the previously isolated, unsulfonated N-methyl enol ester of acetic acid, which decomposes within a few days,[2] the pure crystals of **7** and **8** were unchanged after months of storage in a desiccator over phosphorus pentoxide. Spectral tests further revealed no rearrangement or other

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(1) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961); *Tetrahedron Suppl.*, **8**, 321 (1966).

(2) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 1007 (1961); *Tetrahedron Suppl.*, **7**, 415 (1966).

(3) It has recently been found that enol esters from the N-ethylbenzisoxazolium cation (**4**) are stable,[4] and acylating agents have been isolated also from derivatives of **4**.[5,6]

(4) D. S. Kemp and R. B. Woodward, *Tetrahedron*, **21**, 3019 (1965).

(5) S. Rajappa and A. S. Akerkar, *Chem. Commun.*, 826 (1966).

(6) D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.*, **89**, 2743 (1967).

(7) The esters from N-arylisoxazolium salts were found to be especially susceptible to intramolecular acyl migration *via* the anion.[8]

(8) R. B. Woodward, D. J. Woodman, and Y. Kobayashi, *J. Org. Chem.*, **32**, 388 (1967).

(9) R. B. Woodward and D. J. Woodman, *ibid.*, **31**, 2039 (1966).

(10) R. B. Woodward and D. J. Woodman, *J. Am. Chem. Soc.*, **88**, 3169 (1966).

(11) The N-*t*-butylketoketenimine **7** does not react as rapidly with carboxylic acids as do those from previously studied isoxazolium salts.

(12) Elemental analyses and spectral data are in accord with the expected structures **7** and **8**.

(13) It is unlikely that the source of the difficulty is the presence of nucleophilic contaminants in the solvents. The water product **9** is detectable with undried solvents, but purification to remove basic impurities and drying of solvents do not improve the results. Moreover, nmr spectral tests show similar peaks from unidentified side products with both nitromethane and acetonitrile as solvents for acetic acid. The possibility that these contaminants arose from rearrangement or other decomposition of the product ester was ruled out by control experiments which established that the product was stable to the reaction conditions alone or in combination with either starting material.

decomposition of solutions of **7** in organic solvents after 1 week at room temperature. Since the rearrangement of the less stable esters from other isoxazolium salts is subject to basic catalysis,[2,8] it is also noteworthy that the N-*t*-butyl enol esters are not highly sensitive to base.[14] However, these results do not establish whether the *t*-butyl substituent merely causes rearrangement to be extremely slow or if the enol esters are thermodynamically favored relative to the rearrangement products.

The potential utility of the new esters as acylating agents was tested in a reaction of **8** with benzylamine. Equivalents of the reactants were combined in various organic solvents, and, in each case, the solvent was removed under reduced pressure the next day. Separation of the freely water-soluble by-product **9** from the residue with a few small portions of water left better than 98% yield of pure carbobenzoxyglycylbenzylamide in each test.

$$\mathbf{8} + C_6H_5CH_2NH_2 \longrightarrow C_6H_5CH_2OCONHCH_2CONHCH_2C_6H_5 + \underset{\mathbf{9}}{CH_3COCH_2CONHC(CH_3)_3}$$

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[14] For example, **8** was recovered in better than 90% yield after 24 hr in dry 2-picoline.

[15] A portion of this investigation was carried out during the tenure of a predoctoral fellowship from the National Institute of General Medical Sciences, U. S. Public Health Service. This work was also supported by a grant from the National Institutes of Health.

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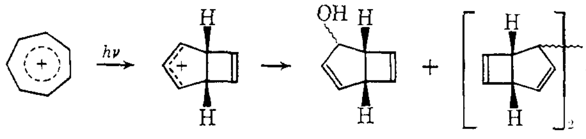
Photolysis of Triphenylcarbonium, Tropylium, and Triphenylcyclopropenium Ions

Sir:

Although the visible and ultraviolet spectra of various carbocationic species have been duly recorded and theoretically treated,[1] the question of product formation from excited carbonium ions has been neglected. In pursuing a program concerned with photolysis of charged carbon species, we have examined the nature of the substances formed during ultraviolet irradiation of tropylium (I), triphenylcyclopropenium (II), and triphenylcarbonium (III) ions, the first carbocationic cases investigated from the standpoint of product development.[2] In the first case (I), photogeneration of the [3.2.0] valence bond isomer Ia of the aromatic system "Dewar tropylium ion") apparently controls the over-all reaction course. In the other systems coupling emerges as an important process;[3] however, depending on solvent and other factors, additional modes of reaction are also observed.

After irradiation in 5% aqueous sulfuric acid for 10 min with a Hanovia 450-W high-pressure lamp (Vycor filter), 42% of the tropylium ion[4] (fluoroborate salt, λ_{max} 217 and 273 mμ)[5] was consumed, giving rise to 58% yield (based on unrecovered starting material) of bicyclo[3.2.0]hepta-3,6-dien-2-ol (IV) and the corresponding ether V, colorless liquids interconvertible in dark reactions. Verification of structural assignments made initially by ir, uv, and nmr methods consisted of chromic acid oxidation of alcohol IV to the corresponding ketone, which possessed properties indistinguishable from those reported for the authentic material.[6]



I Ia IV V

We believe that irradiation of tropylium ion produces to a large extent the valence bond isomer Ia, a highly reactive allylic carbonium ion which readily captures solvent water, producing the bicyclic alcohol IV. That the bicyclic materials IV and V in fact arise by irradiation of tropylium ion, and not the corresponding alcohol, is indicated by (a) the calculated equilibrium constant in 5% sulfuric acid (2.7 × 10^{-4}% covalent) and (b) the dissimilar nature of the products formed when irradiations were carried out in ethanol without added acid, where tropylium perchlorate or bromide is almost completely converted to tropyl ethyl ether (λ_{max} 206 and 254 mμ). After irradiation of the resulting solution for 10–15 min, there was formed a complex mixture of substances, including ditropyl (VI)[7] and its secondary irradation product, which on the basis of (i) catalytic reduction to bicycloheptyl and (ii) mass ($M^+ = 182$), uv (λ_{max} 212 mμ (ϵ 13,400), 264.5 (3200), and 339 (7300)), and nmr (eight olefinic hydrogens at τ 3.6 (triplet) and 3.9 (two doublets), two olefinic hydrogens at τ 4.7 (quartet); and four methylene hydrogens at τ 7.45 and 7.7 (doublets)) spectral properties is regarded as the hexaene isomer VII, formed by twofold photochemical suprafacial 1,7-hydrogen migration. An ethoxylated ditropyl isomer and tropyl ethyl ether were identified, and some troponoid material was also formed. None of the aforementioned substances was formed detectably during irradiation of tropylium ion in 5% aqueous acid.[8]

VI VII

In the cyclopropenium ion[9] system (II) irradiation induces the cation to form ultimately a benzenoid product, apparently by means of a coupling process. A 4-hr photolysis of triphenylcyclopropenium ion (2.0 × 10^{-3}% covalent) in 10% aqueous sulfuric acid with a Hanovia high-pressure lamp (Corex filter) gave hexaphenylbenzene in 49% yield (92% yield based on

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[1] For a review, see S. F. Mason, *Quart. Rev.* (London), **15**, 335 (1961).

[2] We have been able to locate in the literature only one possible prior example, the observation that 9-phenylfluorene was isolated after trityl perchlorate had lain on a desk top for 15 days [H. Dauben, Jr., *J. Org. Chem.*, **25**, 1442 (1960)].

[3] Coupling phenomena have also been encountered in anionic types: E. E. van Tamelen, J. I. Brauman, and L. E. Ellis, *J. Am. Chem. Soc.*, **87**, 4964 (1965); **89**, 5073 (1967).

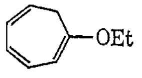
[4] W. von E. Doering and L. H. Knox, *ibid.*, **76**, 3203 (1954).

[5] H. J. Dauben, F. A. Gadecki, K. M. Harmon, and D. L. Pearson, *ibid.*, **79**, 4557 (1957).

[6] P. R. Story and S. Fahrenholz, *ibid.*, **87**, 1623 (1965). These investigators also reported the lithium aluminum hydride reduction of ketone to uncharacterized dienols, which were further reduced to corresponding known saturated alcohols.

[7] W. von E. Doering and L. H. Knox, *ibid.*, **79**, 352 (1957).

[8] Tropyl ethyl ether is reported to produce on irradiation in *neutral* alcohol medium the isomerization product i: G. W. Borden, O. L. Chapman, R. Swindell, and T. Tezuka, *ibid.*, **89**, 2979 (1967).



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[9] R. Breslow, P. Gal, H. W. Chang, and L. J. Altman, *ibid.*, **87**, 5139 (1965).