Formation of pyridines from *N*-methylpyrimidinium iodide and enaminoesters

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The reaction of *N*-methylpyrimidinium iodide with enaminoesters yields a mixture of 3-ethoxycarbonyl-2-methylpyridine and 3,5-diethoxycarbonyl-2,6-dimethylpyridine. Mechanisms of the transformations of the pyrimidine ring found are suggested.

Key words: *N*-methylpyrimidinium iodide; enaminoesters; ring transformation; pyridines, β-substituted.

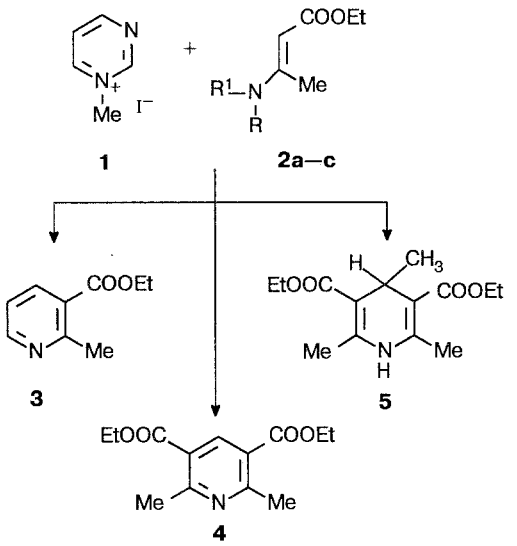
Pyrimidine derivatives typically undergo nucleophilic addition at positions 4, 6, and 2. The reactions with O- and N-nucleophiles (such as hydroxide ion, amide ion, or amines, hydrazines *etc.*), which can finally result in recyclization, simple opening of the pyrimidine ring, or in its opening followed by hydrolytic cleavage to give low-molecular-weight compounds, have been most studied. The reactions of pyrimidine derivatives with C-nucleophiles have been substantially less studied.[1]

Previously it has been reported that the reaction of the nitro derivative of pyrimidine with aliphatic amines and acetone (probably in the form of its enamine) affords *N*-substituted nitroanilines[2] (whose benzene rings being formed thus involve the C—C—C triad), although in one case, the formation of a minor amount of nitropyridine was also detected. Before our studies, the dual interaction of enamines with pyrimidine derivatives has not been observed or discussed in the literature, therefore, it has been of interest to establish the regularities of this interaction.

Enaminoesters[3,4] may be simultaneously regarded as hetero analogs of the allylic anion and as alkenes containing an electron-donating amino group, whose reaction with pyrimidine derivatives may occur as cycloaddition or involving the β-carbon atom. In fact, we found that boiling *N*-methylpyrimidinium iodide (**1**) with enaminoesters (**2a—c**) in pyridine or MeCN yields a mixture of 3-ethoxycarbonyl-2-methylpyridine (**3**) (up to 25 %), 3,5-diethoxycarbonyl-2,6-dimethylpyridine (**4**) (up to 3 %), and 3,5-diethoxycarbonyl-1,4-dihydro-2,4,6-trimethylpyridine (**5**) (up to 3 %) (see Scheme 1). No other reaction products or the starting compounds were detected, along with compounds **3—5** and resin.

We suggested that pyridine **3** can result from two reaction pathways: the electrocyclic mechanism and cycloaddition, *i.e.*, similarly to the previously suggested schemes for the transformation of *symm*-triazine through the action of enaminones.[5,6]

Scheme 1



R = R¹ = H (**a**); R = H, R¹ = Me (**b**); R = R¹= Me (**c**).

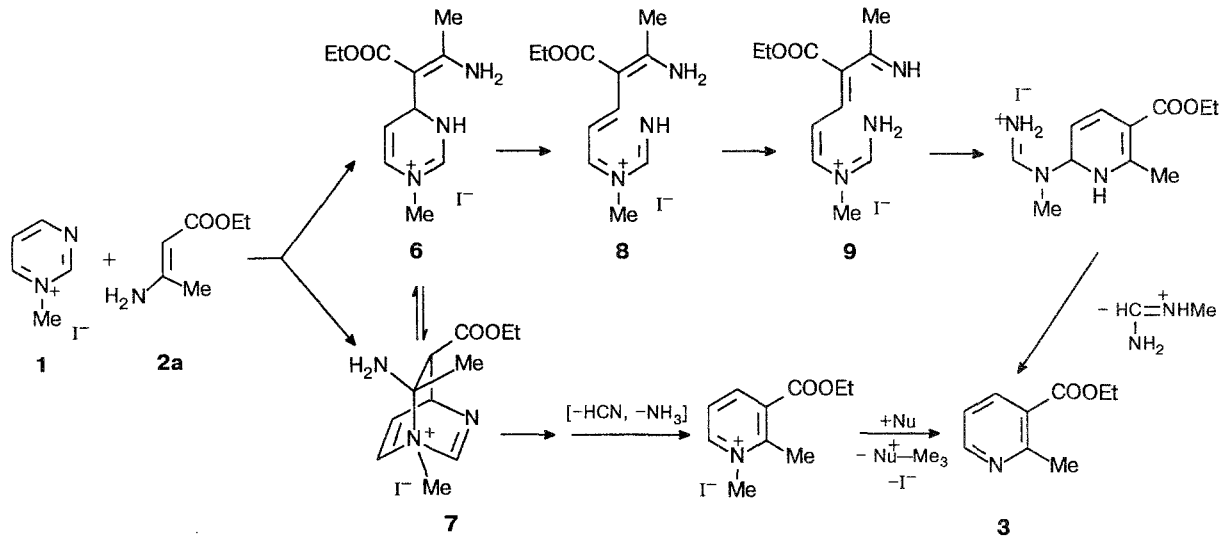
Therefore, we could roughly evaluate the contribution of cycloaddition by comparing the yields of pyridine **3** in the reactions of **1** with ethyl β-aminocrotonates **2a,c**, since in the case of **2c**, the nitrogen atom cannot be incorporated in the pyridine ring formed according to the electrocyclic mechanism.

The yield of compound **3** in the reaction of **1** with **2c** proved to be only 4 %. This means that the pyridine formed in the reaction of **1** with **2a** probably only partially results from cycloaddition, while most of it is produced *via* the electrocyclic mechanism. Based on these data we suggest the following scheme of the formation of 3-ethoxycarbonyl-2-methylpyridine **3** from compounds **1** and **2a** (Scheme 2).

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1318—1321, July, 1995.

1066-5285/95/4407-1272$12.50

Scheme 2



The aromatic ring in the *N*-methylpyrimidinium cation is activated with respect to both nucleophilic attack by the β-carbon atom of enamine **2a** and cycloaddition in the inverted Diels—Alder reaction. The first step of the interaction between compounds **1** and **2a** probably affords an equilibrium mixture of two intermediates **6** and **7**. Then the addition product **6** undergoes electrocyclic cleavage to give heteropolyene **8**. Its subsequent cyclization with the elimination of *N*-methylformamidinium cation yields pyridine **3**. Simultaneously the bicyclic adduct **7** is converted into pyridine **3** with abstraction of hydrogen cyanide and ammonia, as we have suggested previously for other models.[2,5,6]

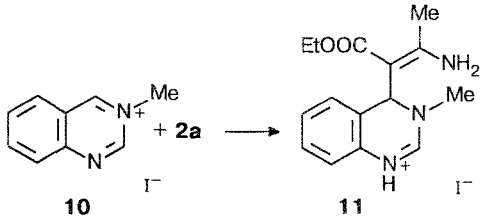
The mechanism of the reaction discovered by us depends slightly on the number of methyl groups at the nitrogen atom of the enaminoester. In fact, the yield of pyridine **3** in the reaction of **1** with ethyl aminomethylcrotonate **2b** is 8 %. In this case, unlike the reaction with enaminoester **2a**, pyridine **3** apparently results from cycloaddition to a greater extent.

In the case of enaminoesters **2b,c**, an alternative route for the closure of the heteropolyene exists in the step of intermediates **8** and **9**; the closure may occur at the β′-carbon atom of the enamine fragment of the intermediate formed from heteropolyene **8** or **9** by tautomeric transformation. However, this process does not occur, which is confirmed by the absence of derivatives of *ortho*-aminobenzoic acid in the reaction products. This distinguishes the reaction found from the ring transformation of nitropyrimidine through the action of acetone and amines to give *N*-substituted nitroanilines[2] and from the ring transformation of *symm*-triazine through the action of hydrochlorides of *N*-substituted enaminones to give *N*-substituted 4-aminopyridines,[5] which involve incorporation of C—C—C triads of atoms of enamines. This behavior of *N*-methylpyrimidinium salt **1** is apparently caused by the fact that the unsubstituted pyridinium ring and the corresponding fragments of the intermediates resulting from its cleavage are not sufficiently electron-deficient.

Although we were not able to obtain direct evidence of the formation of type **6** compounds, we attempted to isolate the products of the addition of **2a** to a model compound containing a pyrimidinium ring. We chose 3-methylquinazolinium iodide (**10**),[7] for which stable adducts with C-nucleophiles[8] are known, but ring transformation of the type under consideration is rather difficult to imagine, as the model compound.

In fact, the reaction of compound **10** with ester **2a** in MeCN or in MeOH was found to give adduct **11** in a quantitative yield (Scheme 3).

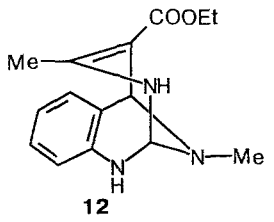
Scheme 3



The addition of the C-nucleophile, as in the scheme of the ring transformation of *N*-methylpyrimidinium iodide, occurs at the "soft" position 4, rather than at the "hard" position 2.

The key signals of the H(C-4) and H(C-2) protons and the signals of the C-4 and C-2 carbon atoms in the NMR spectra of adduct **11** were identified based on the analysis of ^{1}H NMR spectra (recorded at 400 MHz) and using the ^{13}C NMR spectra recorded with the partial $^{13}C\{^1H\}$ decoupling. The final assignment of the signals was carried out by a comparison with the similar

signals in the spectra of the adducts of 3-methylquinazolinium iodide **10** with 2-methylbenzothiazolium and 2-methylindoleninium quaternary salts, whose structures have been determined by us previously using the NOESY two-dimensional spectra.[8] This comparison makes it possible to completely rule out the bicyclic structure of the heterocyclic part of the adduct (of type **12**), which have been suggested by some authors, while interpreting the data on transformations of azines (see, for example, Ref. 9).



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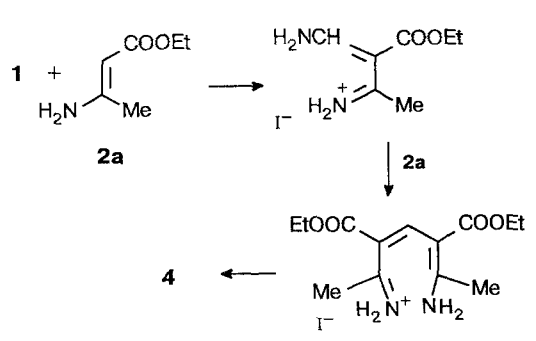
When adduct **11** is boiled in pyridine or in MeCN, no low-polarity products of the desired structure were formed. This is a further reason in favor of the crucial role of the electrocyclic mechanism (shown in Scheme 2) in the reactions of enaminoester **2a** with the pyrimidinium nucleus. In the case of adduct **11**, this process cannot occur.

In parallel with pyridine **3**, the conversion of *N*-methylpyrimidinium iodide **1** into 3,5-diethoxycarbonyl-2,6-dimethylpyridine **4** occurs. In the absence of **1**, when **2a** is merely heated in pyridine or in MeCN, the latter compound is not formed. In view of this fact and taking into account the fact that *symm*-triazine can be used for aminomethylation of the type of Mannich reaction,[6] we assume that the first step of the process in question is probably aminomethylation of **2a** with *N*-methylpyrimidinium iodide **1**. It is followed by the condensation with the second molecule of **2a** and cyclization to give the symmetrical pyridine **4** (Scheme 4).

Scheme 4



In addition to pyridines **3** and **4**, 3,5-diethoxycarbonyl-1,4-dihydro-2,4,6-trimethylpyridine (**5**) was detected among the reaction products in all cases. This compound is not formed in the absence of **1**, when **2a** is merely boiled in pyridine or in MeCN. It is likely that dihydropyridine **5** appears as a by-product in the formation of pyridine **4**, however, it is difficult to make suggestions concerning the mechanism by which it is produced.

The structures of all of the compounds obtained were confirmed by NMR spectroscopy (although we present only the spectra of the previously unknown adduct **11**) and by comparing their physicochemical characteristics with those described previously (for **3**—**5**). The structure of **5** was also confirmed by a comparison with a specimen of the authentic structure.

Thus, the reaction of *N*-methylpyrimidinium iodide with the enaminoesters studied occurs only with the incorporation of the C—C—N triad of atoms of enaminoesters and affords pyridine derivatives.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) using DMSO-d_6 as the solvent and tetramethylsilane as the internal standard. The TLC monitoring was carried out on DC-Alufolien Kieselgel 60 F_{254} plates.

Reaction of *N*-methylpyrimidinium iodide (1) with enaminoesters (2a—c). *a.* A mixture of 1 mmol of salt **1** and 1 mmol of ethyl aminocrotonate **2a** in 3 mL of anhydrous MeCN or pyridine was boiled with reflux for 6 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted several times with a benzene—AcOEt mixture, 1 : 1. The extract was again concentrated *in vacuo* and chromatographed on a column with silica gel (L-40/100 μm, using benzene—AcOEt, 1 : 1, as the eluent) to give 3-ethoxycarbonyl-2-methylpyridine **3**, yield 20—25 %, m. p. of the picrate 145—146 °C (*cf.* Ref. 10); 3,5-diethoxycarbonyl-2,6-dimethylpyridine **4**, yield 3 %, m. p. 71—72 °C (*cf.* Ref. 6); and 3,5-diethoxycarbonyl-1,4-dihydro-2,4,6-trimethylpyridine **5**, yield 3 %, m. p. 127—129 °C (*cf.* Ref. 11). The melting point of a mixture of compound **5** with an authentic specimen is undepressed.

b. A mixture of 0.7 mmol of **1** and 1 mmol of ester **2b** in 3 mL of anhydrous pyridine was boiled with reflux for 6 h. The mixture was treated as described in procedure *a* to give pyridines: **3** (yield 8 %), **4** (yield 1 %), and **5** (yield 1 %).

c. The reaction of salt **1** with ester **2c** was carried out similarly to procedure *b* to give pyridines: **3** (yield 4 %), **4** (yield 1 %), and **5** (yield 1 %).

4-[(1-Aminoethylidene)ethoxycarbonylmethyl]-3,4-dihydro-3-methylquinazolinium iodide (11). A mixture of 0.27 g (1 mmol) of *N*-methylquinazolinium iodide **10** and 0.25 mL (2 mmol) of ethyl aminocrotonate **2a** in 1 mL of MeOH was kept at 20 °C for 1 day and cooled. The precipitate was filtered off and washed with MeOH to give 0.36 g (96 %) of adduct **11**, m. p. 190—193 °C (dec.). ^{1}H NMR, δ: 0.85 (t, 3 H, Me, J = 7.1 Hz); 2.26 (s, 3 H, Me); 3.10 (s, 3 H, NMe); 3.77 (m, 2 H, CH_2, J = 7.1 Hz, J = −11 Hz); 5.81 (s, 1 H, H(C-4)); 6.96 (two d, 2 H, H(C-5) and H(C-8), J = 7.6 Hz); 7.10 and 7.21 (two m, 2 H, H(C-6) and H(C-7), J = 7.6 Hz); 7.59 (br.d, 1 H, NH, J = 3.7 Hz); 8.42 (s, 1 H, H(C-2)); 8.69 (br.d, 1 H, NH, J = 3.7 Hz). ^{13}C NMR, δ: 13.69 ($\underline{C}H_3CH_2$, J = 126.8 Hz); 20.34 ($\underline{C}H_3CH$=, J = 128.0 Hz); 38.48 ($\underline{C}H_3N$, J = 141.4 Hz); 57.26 (C-4, J = 142.6 Hz); 58.31

($CH_3\underline{C}H_2$, J = 146.7 Hz); 91.57 (C=CMe); 115.42 (C-8, J = 160.8 Hz); 123.60 (C-10); 126.24 (C-6, J = 163.7 Hz); 126.52 (C-7, J = 160.8 Hz); 128.07 (C-5, J = 162.0 Hz); 130.21 (C-9); 148.62 (C-2, J = 200.7 Hz); 162.59 (C=CMe); 167.90 (COOEt). Found (%): C, 45.26; H, 5.08; N, 10.62. $C_{15}H_{20}IN_3O_2$. Calculated (%): C, 44.90; H, 5.02; N, 10.47.

References

1. H. C. van der Plas, *Heterocycles,* 1978, **9**, 33.
2. S. P. Gromov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1102 [*Russ. Chem. Bull.*, 1994, 1041 (Engl. Transl.)].
3. Ya. F. Freimanis, *Khimiya enaminoketonov, enaminoiminov, enaminotionov* [*The Chemistry of Enaminoketones, Enaminoimines, Enaminothiones*], Zinatne, Riga, 1974, 274 pp. (in Russian).
4. R. G. Pearson, *Symmetry Rules for Chemical Reactions,* J. Wiley & Sons, New York, 1976, Chapter 4, 5.
5. S. P. Gromov, D. V. Yashunskii, R. S. Sagitullin, and Yu. G. Bundel', *Dokl. Akad. Nauk SSSR,* 1987, **292**, 364 [*Dokl. Chem.*, 1987 (Engl. Transl.)].
6. S. P. Gromov, D. V. Yashunskii, R. S. Sagitullin, and Yu. G. Bundel', *Khim. Geterotsikl. Soedin.*, 1992, 1243 [*Chem. Heterocycl. Compd.*, 1992 (Engl. Transl.)]
7. D. J. Fry, J. D. Kendall, and A. J. Morgan, *J. Chem. Soc.*, 1960, 5062.
8. S. P. Gromov, and M. A. Razinkin, *Khim. Geterotsikl. Soedin*, 1992, 662 [*Chem. Heterocycl. Compd.*, 1992 (Engl. Transl.)].
9. Y. Tohda, T. Kawara, M. Eiraku, K. Tani, M. Ariga, and Y. Mori, *Heterocycles,* 1991, **32**, 2079.
10. P. Baumgarten and A. Dornow, *Ber.,* 1939, **72**, 563.
11. W. Traber and P. Karrer, *Helv. Chim. Acta,* 1958, **41**, 2066.

Received January 10, 1995