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EXCHANGE AMINATIONS IN CONVERSIONS OF PYRIMIDINIUM IODIDES TO 2-ALKYLAMINONICOTINIC ACIDS

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Abstract — 1-Alkyl-2-(ethoxycarbonylmethyl)pyrimidinium iodides (**1**) are transformed into 2-alkylaminonicotinic acids (**2**) by reactions with aliphatic primary amines. Two alternative reaction paths are proposed, one of which involves exchange of the amine moieties.

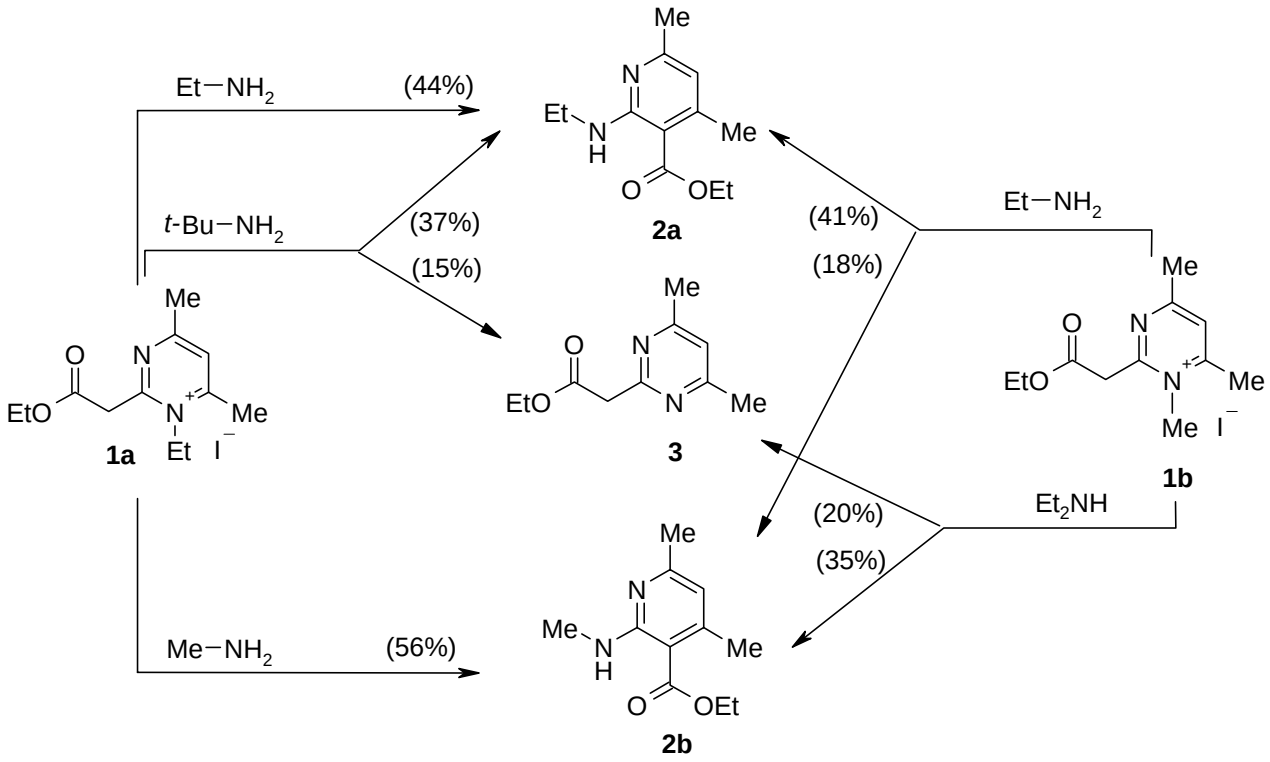
RESULTS AND DISCUSSION

Pyrimidinium salts have long been known to form open chain products under mild conditions by reaction with nucleophiles involving cleavage of N(1)-C(6) bond.[1] Frequently, tandem ring-opening by nucleophile/ring closure leads to insertion of a fragment from the nucleophile into a new ring. An example of such a transformation is the well known Dimroth rearrangement of 1-alkyl-2-aminopyrimidines.[2] Similar rearrangements were used for syntheses from pyrimidinium salts of both neutral pyrimidines[3-5] and of pyridines[6,7] using liquid ammonia and carbanions, respectively.

The transformation of 2-alkylpyrimidinium salts into aminopyridines was previously reported by one of us.[6,8] We have now investigated further this novel route to aminopyridine derivatives, which are of great importance as pharmacophores and as synthons for organic synthesis.[9] Specifically, the present paper describes the reactions of 1,4,6-trialkyl-2-(ethoxycarbonylmethyl)pyrimidinium iodides (**1**) with various amines.

Heating the *N*-ethyl- (**1a**) or *N*-methylpyrimidinium salt (**1b**) (Scheme 1) in a sealed tube at 100 °C with ethanolic ethylamine for 10 h[10] gave in each case ethyl 4,6-dimethyl-2-ethylaminonicotinate (**2a**) as the

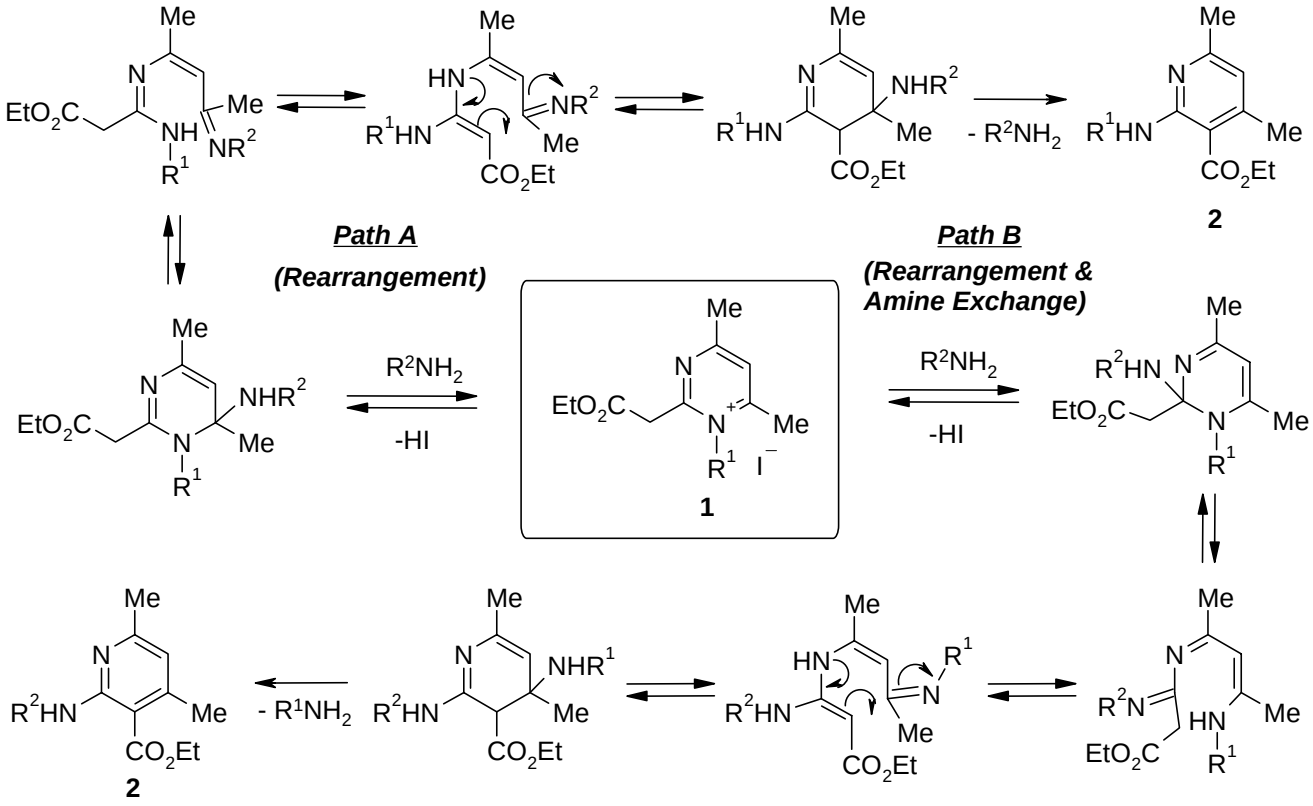
main product. Ethyl 4,6-dimethyl-2-methylaminonicotinate (**2b**) was formed as a by-product in 18% yield from **1b** in the second experiment. Compound (**2b**) (56%) was also isolated as the sole product by heating **1a** with ethanolic methylamine.



Scheme 1

No amine exchange of the type involved in the transformations **1a** to **2b** and **1b** to **2a** was observed for bulky primary or for any secondary amines: thus salts (**1a,b**) reacted with *tert*-butylamine or diethylamine to give only the rearrangement products (**2a,b**) respectively. Pyrimidine (**3**) (*ca.* 20%) was also isolated as a product of the de-alkylations of **1a,b** by *tert*-butylamine and diethylamine, respectively.

These results suggest that the pyrimidinium ring opening occurs by two paths (Scheme 2), involving different positions of initial attack by the amine, which afford different products. Amine attack at the C(6) carbon (Path A) gives a rearrangement product which retains the original amine component. Amine attack on C(2) affords a product incorporating the new amine (Path B). However, as an alternative to Path B, an open-chain intermediate in Path A (Scheme 2) could exchange $EtNH_2$ for R^2NH_2 and thus lead to **2b**. Reversibility of the amine fragments exchange during the imine-enamine isomerizations[11] necessitates a large excess of alkylamine for obtaining high selectivity.



Scheme 2

CONCLUSIONS

We have herein described a new route for the synthesis of 2-alkylaminonicotinic acids and uncovered a novel type of exchange amination in heterocyclic ring transformations, which possesses significant preparative potential.

ACKNOWLEDGMENTS

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10. Transformation of a pyrimidinium salt (**1**) to a 2-alkylaminonicotinic acid (**2**); Typical Procedure. A mixture of pyrimidinium iodide (**1a**) (2 mmol) and 6 mL (10 mmol) of 15% solution of ethylamine in ethanol was sealed in a heavy-wall tube and heated for 10 h at 100 °C. The tube was cooled, opened, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (benzene/acetone, 10:1) to give **2a**. NMR spectra were obtained on a Varian "Mercury 300" spectrometer. GC/MS spectra were obtained on clromass spectrometer (HP 6890 Series Gas Chromatograph, HP 5973 Mss Selective Detector) at EL 70 eV.

2a: an oil; ^{1}H-NMR ($CDCl_3$), δ: 1.23 (t, J = 7.2 Hz, 3H, $NHCH_2C\underline{H}_3$), 1.39 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.35 (s, 3H, 4(6)-$C\underline{H}_3$), 2.44 (s, 3H, 6(4)-$C\underline{H}_3$), 3.51 (dq, J = 7.2 Hz, J = 5.0 Hz, 2H, $NHC\underline{H}_2CH_3$), 4.34 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 6.23 (s, 1H, C(5)$\underline{H}$), 7.73 (br s, 1H, N$\underline{H}$); ^{13}C-NMR ($CDCl_3$), δ: 14.3 (CH_3), 14.9 (CH_3), 23.6 (CH_3), 24.6 (CH_3), 36.0 (NCH_2), 60.4 (OCH_2), 103.7 (C(4)), 114.7 (C(5)), 151.1 (C(6)), 159.0 (C(2)), 160.9 (C(3)), 169.2 (C=O); MS (EI): *m/e* 222 (78), 193 (35), 175 (97), 161 (100), 147 (50), 134 (35), 107 (83), 77 (26).

2b: mp 39-40 °C; ^{1}H-NMR ($CDCl_3$), δ: 1.39 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.38 (s, 3H, 4(6)-$C\underline{H}_3$), 2.43 (s, 3H, 6(4)-$C\underline{H}_3$), 3.04 (d, J = 5.1 Hz, 3H, $NHC\underline{H}_3$), 4.33 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 6.23 (s, 1H, C(5)$\underline{H}$), 7.77 (br s, 1H, N$\underline{H}$); ^{13}C-NMR ($CDCl_3$), δ: 14.4 (CH_3), 23.6 (CH_3), 24.7 (CH_3), 28.2 (NCH_3), 60.5 (OCH_2), 104.0 (C(4)), 114.7 (C(5)), 151.0 (C(6)), 159.6 (C(2)), 160.1 (C(3)), 169.1 (C=O); MS (EI): *m/e* 208 (100), 179 (52), 161 (76), 134 (30), 107 (94), 77 (20).

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