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TETRAACYLATION OF ISOBUTENE : FIRST SYNTHESIS OF 1,3,6,8-TETRAMETHYL-2,7-NAPHTHYRIDINE

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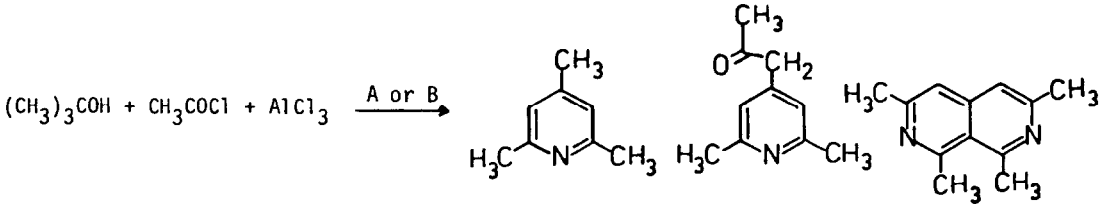
Abstract : *The tetraacetylation of isobutene has been performed in $AlCl_3$/AcCl. Treatment of the crude reaction medium with liquid ammonia yields the title compound.*

It is well documented[1] that isoolefins can undergo stepwise acetylations in a Friedel-Crafts medium. For instance, isobutene has been monoacetylated to give mesityloxide 1, diacetylated to give 2,4,6-trimethylpyrylium salt, and triacetylated to give 4-acetonyl-2,6-dimethylpyrylium salt.[2] These compounds afforded the corresponding pyridines 2 and 3 on treatment with aqueous ammonia[2]. We have found that this nice stepwise acetylation process, which involves the three terminal carbon atoms in the isobutene derivatives, must be reconsidered as follows :

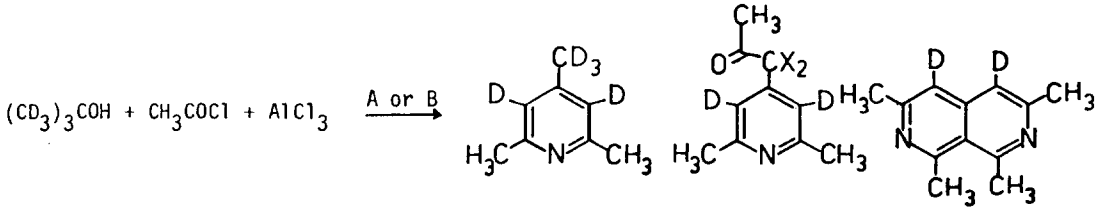
When a mixture of acetyl chloride (1.6 M) and $AlCl_3$ (0.3 M) is treated with t-butanol or t-butylchloride (0.1 M) for 0.5 h. at 35° C., and the crude reaction mixture poured into 300 ML of aqueous ammonia (34 %) with cooling, three heterocyclic bases are obtained after acid and base treatments :2,4,6 trimethylpyridine 2 (36 %), 4-acetonyl-2,6-dimethylpyridine 3 (40 %), and the previously unknown 1,3,6,8-tetramethyl-2,7-naphthyridine 4 (24 %)[3] (scheme 1). The naphthyridine 4 results from the tetraacetylation of the isobutene followed by a double ring closure with ammonia. At this point of the discussion, one can think that this is no more than a further step in the acetylation, due to the experimental conditions, and that isobutene undergoes mono-, di-, tri- and tetraacetylations, as well, in a stepwise manner : the three latter acetylations would lead to the heterocycles 2, 3 and 4.



		2	3	4
Total yield 92 %	(A) NH_4OH (34 %)	36 %	40 %	24 %
Total yield 91 %	(B) liq. NH_3	37 %	traces	63 %

However, the same reaction medium treated with liquid ammonia instead of aqueous ammonia, yields (91 % conversion from t-butanol) 2,4,6-trimethylpyridine 2 (37 %) and naphthyridine 4 (63 %), whereas hardly traces of acetonylpyridine 3 can be detected. It is clear that only traces of the triacetylation product 3 were to be found in the reaction mixture before both treatments and that the acetonylpyridine 3 arises from the cleavage of the geminal diketone under the influence of wter in aqueous ammonia. This is further confirmed by the fact that a very low yield of naphthyridine is obtained when the crude reaction mixture is extracted with water before treatment with aqueous ammonia, as classicaly done in the pyrylium-pyridine work-up[2].

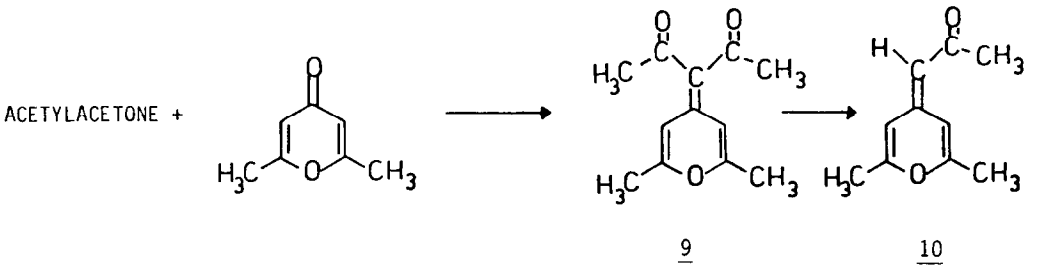
The question arises whether the trimethylpyridine itself could result from acetylcleavage or whether it lies on a reaction pathway parallel to that leading to the tetraacetylation product. Furthermore, since the tetraacetylation is indicated indirectly by the naphthyridine, one might wonder if higher acetylation orders have occurred, which would lead to the naphthyridine after the required number of acetyl cleavages. All of these questions were settled by the use of $(CD_3)_3COH$ as starting material. Treatment with liquid ammonia afforded 35 % 2,6-dimethyl-4-deuteromethyl-3,5-dideuteropyridine 5,[4] trace of 2,6-dimethyl-4-CH_3COCD_2-3,5-dideuteropyridine 6,[4] and 65 % 4,5-dideutero-1,3,6,8-tetramethyl-2,7-haphthyridine 7,[4] whereas treatment with aqueous ammonia yielded 36 % 5, 41 % 2,6-dimethyl-4-acetonyl-3,5-dideuteropyridine 8[4] and 23 % 7. Thus in both cases, pyridines and naphthyridine have deuterium left on the aromatic ring, pointing out clearly that they are not derived from intermediates with higher acetylation order. Compounds 6, which has retained 4 deuterium atoms, does not come from the cleavage of the tetraacetylation product, but accounts for the low concentration of triacetylation product in the medium. In aqueous ammonia, pyridine 8 had lost the deuterium expected to be left on the methylene group.



(B) liq. NH_3	35 % 5	X=D ε % 6	65 % 7
(A) NH_4OH (34 %)	36 % 5	X=H 41 % 8	23 % 7

In summary, it appears that the tetraacetylated intermediate, whatever its precise form, is in a deep potential well which leads to very rapid conversion of all of the triacetylated form, and also prevents any further acetylation. Almost all of the product which could apparently come from triacetylated form results from deacetylation under aqueous conditions. Our results may be

related to the behaviour of the reaction product obtained by treatment of 2,6-dimethyl-γ-pyrone with acetylacetone. It has been reported[5] that the expected product 9 undergoes deacetylation under very mild conditions, and consequently was isolated in very poor yield, the acetylvinyl-pyrone 10 being obtained. So we believe that compound 9, or more likely its protonated form, is a good representation of the tetraacetylation product of isobutene, accounting for its easy deacetylation and the prevention of further acetylation.



9 10

The 2,7-naphthyridine nucleus is in general far from being easy to prepare, as it generally involves multistep syntheses with sophisticated starting material[6]. None of the reported syntheses could be adapted to the synthesis of naphthyridine 4. Thus the tetraacetylation of isobutene followed by treatment with liquid ammonia provides straightforward access to the tetramethyl naphthyridine nucleus. The scope and the limitations of this new reaction[7] are currently under investigation.

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3 - 2,4,6-Trimethylpyridine 2:[8] nmr ($CDCl_3$) : 2.22 (3H,s), 2.45 (6H,s), 6.78 (2H,s) ; ms (70 eV) m/e (%) : 122 (14), 121 (100), 120 (42), 106 (16.5), 79 (19), 77 (10), 39 (16).
4-Acetonyl-2,6-dimethylpyridine 3:[8] nmr ($CDCl_3$) : 2.16 (3H,s),2.48 (6H,s), 3.62 (2H,s), 6.81 (2H,s) ; ms (70 eV) m/e (%) : 163 (20), 121 (100), 106 (4), 77 (16) 51 (5), 43 (62), 39 (7).

The 1,3,6,8-tetramethyl-2,7-naphthyridine 4 was identified as $C_{12}H_{14}N_2$ by exact masse determination. Nmr ($CDCl_3$) : 2.6 (6H,s), 3.05 (6H,s), 7.1 (2H,s) ; ms (70 eV) m/e (%) : 187 (16), 186 (100), 185 (48,5), 171 (12), 144 (7), 115 (8.5), 77 (8.4), 51 (6), 42 (8), 39 (11).

4 - 2,6-Dimethyl-4-deuteromethyl-3,5-dideuteropyridine 5 : nmr ($CDCl_3$) : 2.45 (6H,s) ; ms (70 eV) m/e (%) : 127 (16), 126 (100), 125 (73), 124 (35), 123 (9.4), 111 (13), 84 (32), 83 (39), 82 (19), 81 (18), 80 (20), 79 (11), 56 (11), 55 (11), 54 (14.2), 53 (14.3), 52 (13.3), 43 (16) 42 (35.6), 41 (23), 40 (25.6), 39 (11.5), 29 (10).

2,6-Dimethyl-4-CH_3COCD_2-3,5-dideuteropyridine 6 : This product was obtained as traces. It showed the presence of 4 deuterium in the molecule. Ms (70 eV) m/e (%) : 167 (28.5), 166 (28.5), 165 (42.8), 125 (100), 124 (57), 123 (71), 122 (14).

4,5-Dideutero-1,3,6,8-tetramethyl-2,7-naphthyridine 7 : nmr ($CDCl_3$) : 2.6 (6H,s), 3.05 (6H,s); ms (70 eV) m/e (%) : 189 (16), 188 (100), 187 (84.6), 186 (28), 173 (11), 146 (6), 145 (5), 78 (10), 77 (5), 42 (10).

2,6-Dimethyl-4-acetonyl-3,5-dideuteropyridine 8 : nmr ($CDCl_3$) : 2,16 (3H,s), 2,48 (6H,s), 3,62 (2H,s) ; ms (70 eV) m/e (%) : 165 (21), 123 (100), 122 (25), 79 (8), 43 (67).

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