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A HIGHLY SELECTIVE METHOD FOR THE SYNTHESIS OF SYMMETRICAL TRISUBSTITUTED PYRIDINES USING TRANSITION AND NON-TRANSITION METAL SALTS

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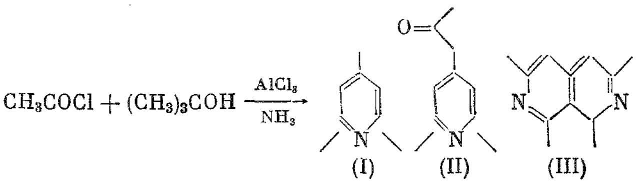
Erre et al. [1] have recently reported the preparation of alkylpyridines by the reaction of AcCl with t-BuOH in the presence of $AlCl_3$ with subsequent treatment of the condensation products by aqueous or gaseous NH_3 to give a mixture of 2,4,6-trimethylpyridine (I), 4-acetonyl-2,6-dimethylpyridine (II), and 1,3,6,8-tetramethyl-2,7-naphthyridine (II) with ~85% total yield; the content of pyridines (I) and (II) in the product was ~35-70% [1].



Attempts to increase the selectivity of this reaction relative to (I) by changing the reagent ratio, conditions and concentration of the Lewis acid were unsuccessful.

A study was carried out on the reaction of C_2-C_6 aliphatic acid chlorides with t-BuOH, isobutylene and NH_3 by the action of transition and non-transition metal salts ($AlCl_3$, $ZnCl_2$, $InCl_3$, $TiCl_4$, $TiCl_3$, WCl_6, $FeCl_3$, $CoCl_2$, $NiCl_2$ and $PdCl_2$) and bimetallic systems $AlCl_3$–$NiCl_2$ and $AlCl_3$–$PdCl_2$ in a search for new catalysts for this reaction which provide for the formation of (I), which has practical importance, and to determine the possibility of using other acid chlorides and isobutylene in this reaction.

The use of isobutylene gives some increase in the total yield of (I)-(III) but with a predominance of (III). The use of bimetallic Lewis acids containing $AlCl_3$, $NiCl_2$ and $PdCl_2$ significantly increased the yield of (I)-(III) and the selectivity relative to (I). Thus, for example, a 1.6:0.1 mixture of acetyl chloride and isobutylene in the presence of 7:3 $AlCl_3$–$NiCl_2$ or $AlCl_3$–$PdCl_2$ with subsequent treatment of the reaction products with NH_4OH gave a mixture of (I)-(III) with total yield of 97%, in which the content of (I) was 88%. In addition to (I), a slight amount of (III) and unidentified higher isobutylene oligomers are formed under these conditions. Among the transition and non-transition metal salts tested, the highest yields of (I) were obtained upon using $InCl_3$ or $ZnCl_2$ as the Lewis acid. The selectivity relative to (I) in the presence of these salts is 97%, while the isobutylene conversion in these experiments was 99%. In light of the availability and ease of obtaining $ZnCl_2$, all the subsequent experiments on the synthesis of substituted alkylpyridines were carried out in the presence of $ZnCl_2$.

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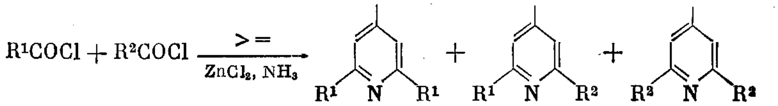
TABLE 1. Effect of the Ratio of the Starting Acid Chlorides on the Yield and Selectivity of Mixed Trialkylpyridines

$CH_3-C\overset{O}{\underset{Cl}{\langle}}$	$C_4H_9-C\overset{O}{\underset{Cl}{\langle}}$	Isobutylene conversion, %	Composition of reaction products, %		
			(I)	(VII)	(V)
1	1	93	12	52	38
1	2	93	7	62	31
1	3	94	—	21	79
2	1	93	15	30	55
3	1	94	25	25	50
4	1	94	36	25	39

Thus, for example, the acid chlorides of acetic, butyric, valeric and caproic acids react with isobutylene and NH_3 in the presence of $ZnCl_2$ to form only 2,6-dialkyl-4-methylpyridines in high yields. The structure of the carboxylic acid chloride in this case has virtually no effect on the yield of the trisubstituted pyridines.

The reaction of two different carboxylic acid chlorides gives a mixture of trisubstituted pyridines containing fragments of both carboxylic acids as the alkyl groups. In particular, acetyl chloride and BuCOCl taken in 1:1 ratio, isobutylene and NH_3 gave (I), 2-butyl-4,6-dimethylpyridine (VII) and 2,6-dibutyl-4-methylpyridine (V), whose total yield and composition varies with change in the ratio of the starting acid chlorides (Table 1). Similarly, mixed trialkylpyridines (VII)-(IX) were obtained from the acid chlorides derived from these acids upon the combined condensation with isobutylene and ammonia.



$R^1 = CH_3$, $R^2 = C_3H_7$ (VII); $R^1 = CH_3$, $R^2 = C_4H_9$ (VIII); $R^1 = C_3H_7$, $R^2 = C_4H_9$ (IX).

EXPERIMENTAL

Acid chlorides derived from 99%-pure aliphatic acids were obtained according to a standard procedure [2]. The alkylpyridines were analyzed on a Khrom-41 chromatograph with a flame ionization detector, 1.2 m column packed with 15% Apiezon on 545 zeolite, and nitrogen gas carrier. The PMR spectra were taken on a Tesla BS-467 spectrometer in $CDCl_3$. The IR spectra were taken neat on a UR-20 spectrophotometer. The mass spectra were taken on an MKh-13-06 mass spectrometer at 70 eV and 200°C ionization chamber temperature.

General Method for the Synthesis of Trialkylpyridines. a) A sample of 1.6 mole acetyl chloride, 0.3 mole $AlCl_3$ and 0.1 mole isobutylene was added to a 100-ml steel autoclave cooled to 0°C in an argon stream. The mixture was maintained for 30 min at 35°C with stirring and then cooled. This mixture was slowly poured into a solution of NH_4OH cooled to 0°C and extracted with three 100-ml portions of ether. The extract was dried with anhydrous $MgSO_4$. Removal of the solvent gave a mixture shown by gas—liquid chromatographic analysis to consist of 34% (I), 35% (II) and 41% (III) with 94% total yield. The indices of these compounds corresponded to reported values [1].

b) The reaction of acetyl chloride and isobutylene in a catalytic system of 7:3 $AlCl_3$—$NiCl_2$ or $AlCl_3$—$PdCl_2$ as described above gave a mixture of (I)-(III) in 97% total yield. The content of (I) in the product mixture was 88% and the content of (II) + (III) was 12%.

c) A sample of 1.6 mole of the corresponding aliphatic acid chloride, 0.2 mole $ZnCl_2$ and 0.1 mole isobutylene was added to a 100-ml steel autoclave cooled to 0°C in an argon stream. The reaction and workup were carried out as described above. The yield and selectivity of the compounds obtained are given in Table 1. The products obtained had the following indices.

2,4,6-Trimethylpyridine (I), bp 170°C (760 mm), n_D^{20} 1.4970. IR spectrum (ν, cm^{-1}): 840, 1020, 1220, 1590, 1610. PMR spectrum (δ, ppm): 2.2 s (3H, CH_3), 2.45 s (6H, CH_3), 6.78 s (2H, CH), M^+ 121. Found, %: N 11.0. $C_8H_{11}N$. Calculated, %: N 11.5.

2,6-Dipropyl-4-methylpyridine (IV), bp 80-85°C (5 mm), n_D^{20} 1.4720. IR spectrum (ν, cm^{-1}): 840, 1020, 1220, 1595. PMR spectrum (δ, ppm): 0.9 (6H, CH_3), 1.58 (4H, CH_2), 2.35 (3H, CH_3), 2.78 (4H, CH_2), 6.92 m (2H, CH); M^+ 177. Found, %: C 81.0; H 10.5; N 7.0. $C_{12}H_{19}N$. Calculated, %: C 81.3; H 10.7; N 7.9.

2,6-Dibutyl-4-methylpyridine (V), mp 54 ± 0.5°C. IR spectrum (ν, cm^{-1}): 840, 1020, 1220, 1590. PMR spectrum (δ, ppm): 0.90 (6H, CH_3), 1.58 m (8H, CH_2), 2.35 m (3H, CH_3), 2.78 (4H, CH_2), 6.92 m (2H, CH); M^+ 205. Found, %: C 81.06; H 10.13; N 7.01. $C_{14}H_{23}N$. Calculated, %: C 81.36; H 10.73; N 7.91.

2,6-Diamyl-4-methylpyridine (VI), mp 90 ± 0.5°C. IR spectrum (ν, cm^{-1}): 840, 1020, 1220, 1590. PMR spectrum (δ, ppm): 0.88 m (6H, CH_3), 1.38 m (12H, CH_2), 2.2 m (3H, CH_3), 2.72 m (4H, CH_2), 6.83 (2H, CH); M^+ 233. Found, %: C 82.0; H 11.09; N 5.91. $C_{16}H_{27}N$. Calculated, %: C 82.4; H 11.59; N 6.01.

d) A mixture of two aliphatic acid chlorides containing 0.8 mole of each, 0.2 mole $ZnCl_2$ and 0.1 mole isobutylene was added to an autoclave cooled to 0°C. The reaction and workup were carried out as described above. The mixture of trialkylpyridines was carried out by vacuum distillation. The yield and composition of the reaction products are given in Table 1. The mixed trialkylpyridines obtained had the following indices.

2-Propyl-4,6-dimethylpyridine (VIII), mp 85-91°C (5 mm), n_D^{20} 1.4570. IR spectrum (ν, cm^{-1}): 835, 1025, 1080, 1220, 1600. PMR spectrum (δ, ppm): 0.90 m (3H, CH_3), 1.58 (2H, CH_2), 2.25 (3H, CH_3), 2.38 (3H, CH_3), 2.78 (2H, CH_2), 6.92 (2H, CH): M^+ 149. Found, %: C 81.4; H 10.0; N 9.0. $C_{10}H_{15}N$. Calculated, %: C 81.1; H 10.07; N 9.4.

2-Butyl-4,6-dimethylpyridine(VII), bp 45 ± 0.5°C. IR spectrum (ν, cm^{-1}): 720, 840, 1020, 1220, 1600. PMR spectrum (δ, ppm): 0.90 m (3H, CH_3), 1.58 m (4H, CH_2), 2.22 (3H, CH_3), 2.38 (3H, CH_3), 2.78 (2H, CH_2), 6.9 (2H, CH); M^+ 163. Found, %: C 80.6; H 10.0; N 8.0. $C_{11}H_{17}N$. Calculated, %: C 80.98; H 10.43; N 8.59%.

2-Propyl-4-methyl-6-butylpyridine (IX), bp 46 ± 0.5°C. IR spectrum (ν, cm^{-1}): 840, 980, 1020, 1220, 1600. PMR spectrum (δ, ppm): 0.95 m (6H, CH_3), 1.58 (6H, CH_2), 2.23 m (3H, CH_3), 2.72 m (4H, CH_2), 6.75 m (2H, CH); M^+ 1.91. Found, %: C 81.4; H 10.6; N 7.01. $C_{13}H_{21}N$. Calculated, %: C 81.68; H 10.99; N 7.33.

CONCLUSIONS

New highly selective catalysts derived from non-transition metal salts ($ZnCl_2$ and $InCl_3$) and bimetallic systems ($AlCl_3$–$NiCl_2$ or $AlCl_3$–$PdCl_2$) were developed which permit the preparation of symmetrical trialkylpyridines in high yield from carboxylic acid chlorides, isobutylene and ammonia.

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