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REACTION BETWEEN $AlCl_3$ σ-COMPLEXES OF CYCLOBUTADIENES AND ETHYLCYANOFORMATE. NOVEL SYNTHESIS OF SUBSTITUTED PYRIDINES.

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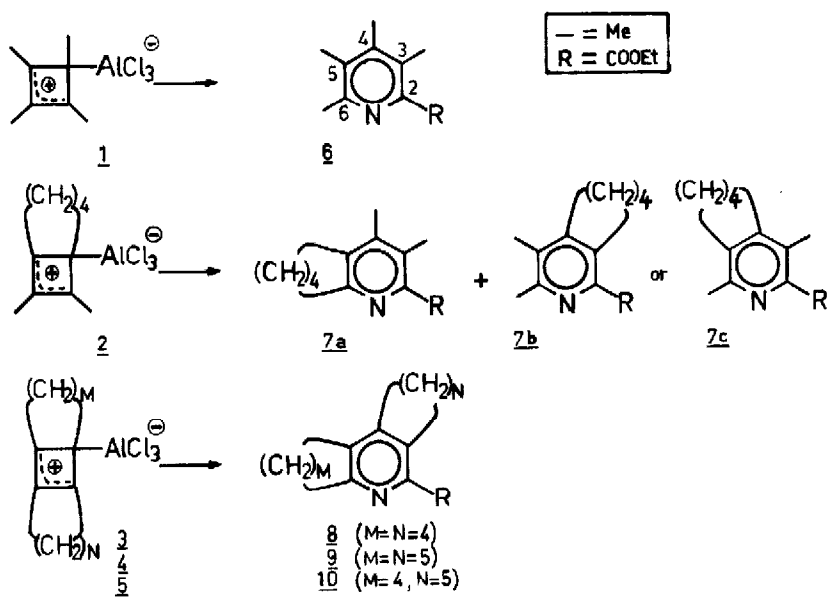
We have developed a new route to some pyridine derivatives through exploitation of the unique properties of the $AlCl_3$ σ-complexes of cyclobutadienes (cyclobutenyl cations)[1-3]. This approach differs totally in concept from other recently developed syntheses such as the cycloaddition of an acetylenic mono- or diester with 1-amino-2-aza-1,3-dienes[4a], nickel catalysed coupling of di-Grignard reagents with 2,6-dichloropyridine[4b], cobalt catalysed reaction between appropriate acetylenes and nitriles[4c] and reaction of α,β-unsaturated aldimines with nitriles[4d].

Reaction at 0-20°C for 0.5-2 hours of 0.6 molar solutions of the $AlCl_3$ σ-complexes 1[1], 2[2] and 3-5[3] in CH_2Cl_2 with 2 equivalents of EtOOCC≡N (added dropwise as a 6 molar solution in CH_2Cl_2) yielded the $AlCl_3$-complexed pyridines,[5] which after appropriate work up[6] gave the free pyridines in

Scheme 1



60% (6), 53% (7), 41% (9) and 40% (9) and 43% (10) isolated yield (Scheme 1). The PMR and CMR chemical shifts are given in the Table.

Table: PMR and CMR (FT) chemical shifts of pyridines 6-10.

	PMR[a]				CMR[b]								
	$-CH_3$		$-CH_2-$		ring C					$-CH_3$		$-CH_2-$	
	3, 4, 5	6	α[c]	other	2	3	4	5	6	3, 4, 5	6[e]	6α[c]	other
6	2.30 2.23 (2x)	2.46			146.3	127.6	144.1	130.7	152.7	14.9 15.2 (2x)	23.2		
7a	2.24 2.09		2.7 (br)	1.8 (br)	146.8	127.2	144.0	131.2	153.1	14.2 14.8		32.4	22.5-26.5 (3s)
7b or 7c[d]	2.09	2.43	?	?									
8			2.5 (br) 2.8 (br)	1.7 (br)	146.0	128.7	144.3	131.5	152.6			32.2	22.0-25.9 (7s)
9			2.8 (br)	1.8 (br)	145.6	133.8	149.6	135.7	159.9			38.2	26.2-31.8 (9s)
10			2.7 (br)	1.7 (br)	146.6	133.2	150.7	129.6	153.8			32.6	22.4-31.7 (8s)

a. in CCl_4, values in ppm relative to internal TMS. Ester absorptions at 4.25-4.36 (q) and 1.37-1.38 (t) ppm.

b. " " " " " " " " " Ester absorptions at 166.1-166.6. (-COO-), 59.9-60.1 ($-CH_2$) and 14.1-14.2 ($-CH_3$) ppm.

c. α: adjacent to the pyridine ring.

d. Due to the low concentration (relative to 7a, see text) ^{13}C assignments could not be made for the minor component (7b or 7c).

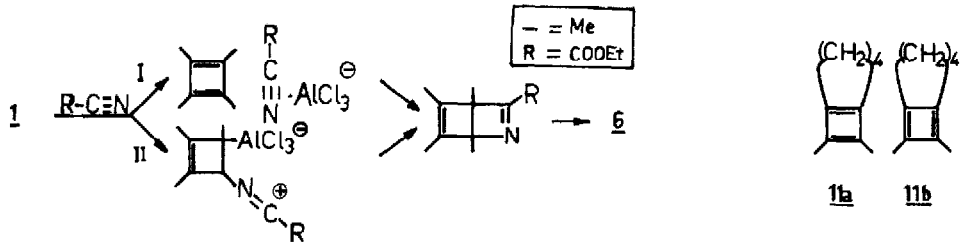
e. Assignment based on comparison with other methylated pyridine derivatives[11].

In the PMR spectrum of 6 the low-field CH_3 signal at 2.46 ppm was assigned to the 6-CH_3 group, in agreement with assignments of other methylated pyridines[7]. The PMR spectrum of mixture 7 displays the signals of only two of the three possible isomers in a 6:1 ratio. These isomers could not be separated[8]. Structure 7a was assigned to the major product in view of the absence of a low-field 6-CH_3 signal (see Table). We have not succeeded yet in deciding whether structure 7b or 7c, both bearing a 6-CH_3 substituent, should be assigned to the minor product. Besides ester absorptions, the PMR spectra of 8-10 display broad signals, arising from the methylene-chain hydrogens. Those centered around 2.5-2.8 ppm were assigned to the $-CH_2$-protons adjacent (α) to the pyridine ring.

In the CMR spectrum of 6 (as for 7-10) the signal of the ring carbon atom with lowest intensity was assigned to C_2[9], whereas assignment of the remaining four signals of the ring carbon atoms was based on predicted chemical shifts[10]. Comparison of the C_3, C_4, C_5 and C_6 signals in the CMR spectra of 7a-9 with those of 6 (see Table) reveals that annelation by six-membered rings (e.g. 7a and 8) has almost no effect on the chemical shifts, whereas annelation by seven-membered rings (e.g. 9) causes down-field shifts of 5.7-7.2 ppm. The CMR spectrum of the reaction product from 5 displays the signals of only one of the two possible isomers. These were assigned to the ethyl ester of 3,4-pentamethylene-5,6-tetramethylene-pyridine-2-carboxylate (10) rather then the isomeric ester of 3,4-tetramethylene-5,6-pentamethylene-pyridine-2-carboxylate, on the basis of the above mentioned relationship for annelation by six- and seven-membered rings (see Table).

As depicted in Scheme 2 for compound 1, two possibilities have to be envisaged for the mechanism of the reactions of σ-$AlCl_3$ complexes 1-5 with EtOOCC≡N.

Scheme 2



In mechanism I, the cyanoformate firstly acts as a base for removing the $AlCl_3$ from the complex. A subsequent Diels-Alder reaction of the generated cyclobutadiene with possibly the same cyanoformate, yields an $AlCl_3$-complexed dewarpyridine. Because of intrinsic lack of stability[12] and as well as catalysis by $AlCl_3$, rearrangement to an $AlCl_3$ - complexed pyridine[5] occurs. Removal of the $AlCl_3$ by base leads to the products observed. In mechanism II, initial nucleophilic attack of the nitrogen atom of EtOOCC≡N at the terminal carbon atoms of the allylic system of 1 is involved. Formation of a dewarpyridine intermediate occurs subsequently through ring closure of the imino-carboniumion with expulsion of $AlCl_3$.

In mechanism II the positive charge developed on the carbon atom of the nitrile is destabilised by the ester group, which makes this mechanism unlikely. Moreover, if reaction of 1 with EtOOCC≡N were to proceed via mechanism II, one would expect an analogous reaction of 1 with a nitrile such as MeC≡N, in which the positive charge can be stabilised by the methyl group. However, reaction of 1 with MeC≡N does not yield a pyridine derivative, instead the major product[13] is the dimer of tetramethylcyclobutadiene[1b]. Hence the initial step in this reaction consists of the generation of a cyclobutadiene from 1 and not of a nucleophilic attack by the nitrogen atom on a cyclobutenyl carbon atom. Apparently, in contrast to EtOOCC≡N, MeC≡N is not a sufficiently good dienophile to form a Diels-Alder adduct with cyclobutadiene.

The reactions of 2-5 with EtOOCC≡N likely proceed in a fashion similar to that of 1. For the cyclobutadiene generated from 2 two valence isomers 11a and 11b are possible[14]. Trapping of 11 with MeOOCC≡CCOOMe has been reported[2] to yield only the Diels-Alder product derived from 11a. Similar Diels-Alder reaction of EtOOCC≡N with 11a would give rise to the formation of two dewar-pyridine intermediates and subsequently the pyridine derivatives 7a and 7b.[15] For the reactions of 3-5 with EtOOCC≡N only the involvement of cyclobutadiene valence isomers with endo-cyclic double bonds can ultimately yield the products observed[16].

This topic is currently under further investigation.

Acknowledgement

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3. Complexes 3, 4, and 5 are prepared from equimolar quantities of $AlCl_3$ and 1,7-cyclododecadiyne, 1,8-cyclotetradecadiyne and 1,7-cyclotridecadiyne, respectively. P.B.J. Driessen and H. Hogeveen, unpublished results.
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5. In a separate experiment it was shown that complexation of 6 by 1 equivalent of $AlCl_3$ causes down-field shifts of 0.2-0.5 ppm for the $-CH_3-$ and 0.26 ppm ($-CH_2-$) and 0.07 ppm ($-CH_3$) for the ester-signals.
6. The reaction mixtures were poured into alkaline water, extracted with pet. ether and the organic layers extracted with 1N HCl. The acid layers were made weakly alkaline and extracted with pet. ether. Drying and evaporating the solvents afforded the pyridine derivatives. An analytically pure sample of 6 was obtained after prep. tlc (SiO_2 plate) and recrystallisation (pentane); m.p. 39.5-40.5°C, mass spectrum m/e = 207 (parent peak), correct elemental analysis. The molecular formulae of 7-10 (oils) were determined using high-precision mass spectrometry (parent peaks); 7: found 233.146 (calc. 233.142), 8: found 259.156 (calc. 259.157), 9: found 273.175 (calc. 273.173), 10: found 287.187 (calc. 287.189). I.R. (6-10): 1730 cm^{-1} (ester c=o). U.V. λ_{max} (CCl_4); 6: 276 nm (log ε = 3.74); 7: 279 nm (log ε = 3.60), 8: 280 nm (log ε = 3.57), 9: 280 nm (log ε = 3.62), 10: 276 nm (log ε = 3.59).
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8. Methods attempted were prep. tlc (SiO_2 plate) and glc (200° C, SE-30 column). Prep. tlc gave no separation, with glc the minor component appeared as a shoulder on the peak of the major one.
9. The C_2 atoms in 6-10 do not bear a $-CH_3$ (or $-CH_2-$) substituent. The relaxation times will therefore be longer and hence the intensity of the C_2 signals smaller then those of C_3-C_6.
10. To this end substitution parameters of methylated pyridines[11] were used. The effects of ester substitution and steric hindrance of $-CH_3$ groups at adjacent ring carbon atoms were taken from comparably substituted benzenes[11].
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13. A. mixture of minor products, whose structures have not yet been clarified, was isolated by acid extraction (see note 6 for procedure).
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15. This only holds if an equilibirum between the isomeric pyridines does not exist under the reaction conditions. Experiments to verify this are under way.
16. Experiments are under way to trap the cyclobutadienes from 3-5 with MeOOCC≡CCOOMe.