HAMMICK CYCLIZATIONS STUDIES ON THE MECHANISM OF THE HAMMICK REACTION[1]

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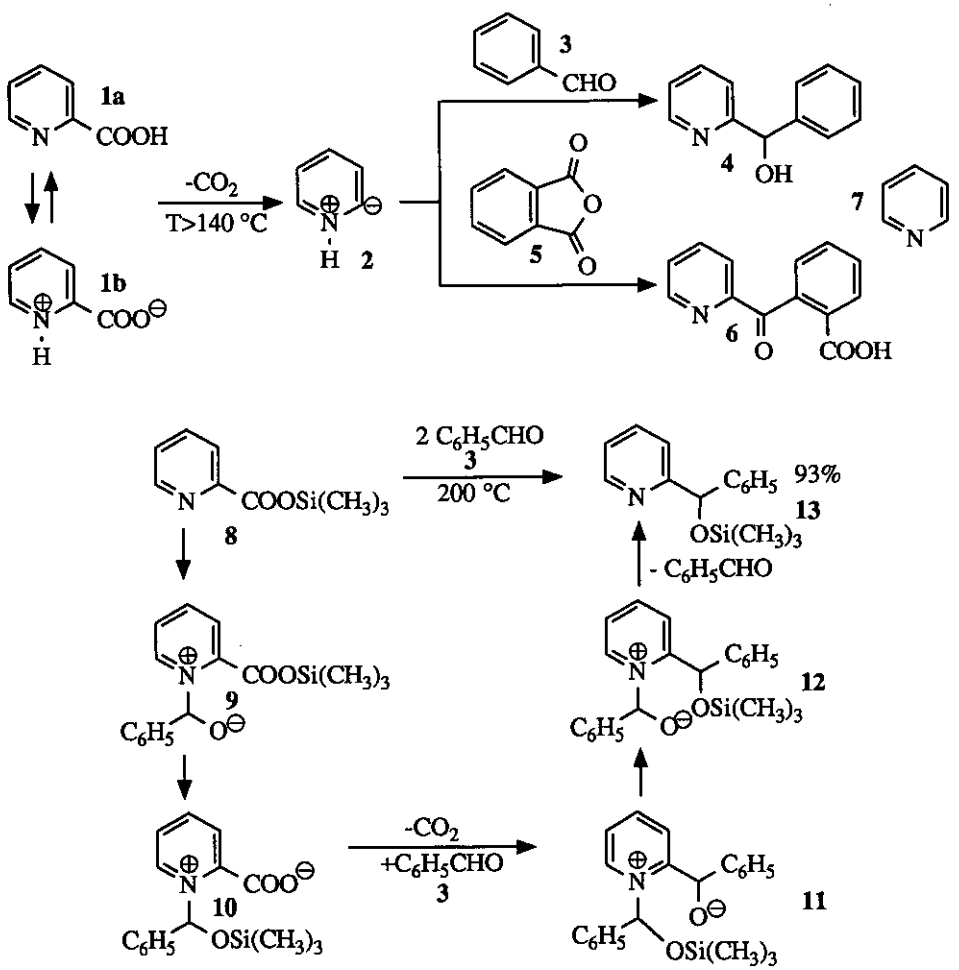
Dedicated to A. R. Katritzky on the occasion of his 65th birthday

Abstract - Heating of 3-hydroxypicolinic acid with the acetylketene precursor 2,2,4-trimethyldioxin-4-one, ethyl acetoacetate or ethyl 2-cyclopentanonecarboxylate leads *via* the 3-*O*-acylated 3-hydroxypicolinic acids, which cannot be isolated, and subsequent decarboxylation to the corresponding Hammick cyclization products in up to 25% yield besides 3-hydroxypyridine. In the case of 3-aminopicolinic acid the 3-(3-oxobutyrylamido)picolinic acid can be isolated but gives on heating only 3-aminopyridine and 3-(3-oxobutyrylamido)pyridine albeit none of the anticipated Hammick cyclization products. The Hammick cyclization reactions, side reactions and reaction mechanisms are discussed.

INTRODUCTION

During studies with heterocyclic bases, Hammick[2,3] discovered that picolinic acid (**1a**) or (**1b**) decarboxylates at T>140 °C to form an intermediate zwitter-ion (**2**), which reacts with the carbonyl groups of benzaldehyde (**3**) or phthalic anhydride (**5**)[4] to give the corresponding adducts (**4**) and (**6**) in yields of up to 60% as well as pyridine (**7**). These yields are usually not exceeded since the postulated reactive zwitter-ion intermediate (**2**) always rearranges to a large extent to pyridine (**7**). Analogously other heterocyclic α-carboxylic acids such as isoquinoline-1- or quinoline-2-carboxylic acid react with aldehydes or ketones to the corresponding heterocyclic alcohols and isoquinoline or quinoline.[5]

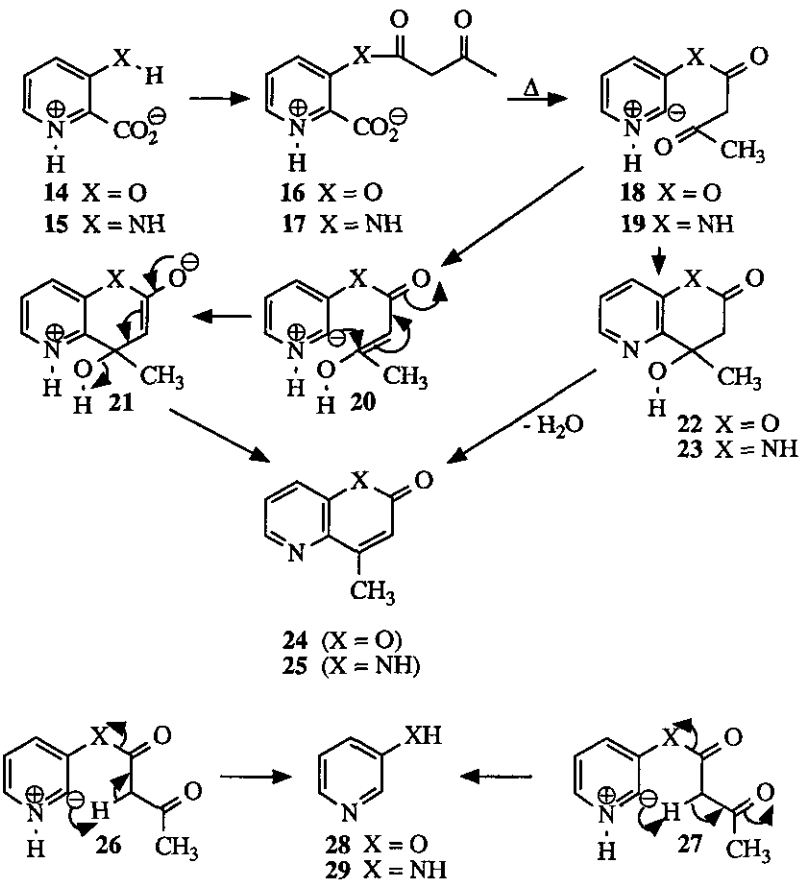
The yields of adducts can be raised considerably according to Effenberger and König[6] when silylated picolinic acid (**8**) is reacted at 200 °C with 2 equivalents of benzaldehyde (**3**) to give *via* the adduct (**9**) and migration of the silylgroup the intermediate (**10**). Hammick reaction of **10** with benzaldehyde to generate **11** is followed by a second migration of the silylgroup to give **12**, which eliminates benzaldehyde to form the silylated Hammick-product (**13**) in 93% yield.[6]



INTRAMOLECULAR HAMMICK REACTIONS

Since as yet only intermolecular Hammick reactions have been described, we wondered whether intramolecular Hammick reactions (cyclizations) might not only provide higher yields of the anticipated Hammick cyclization products but would also give insight into the reaction mechanism of the Hammick-reaction. As model

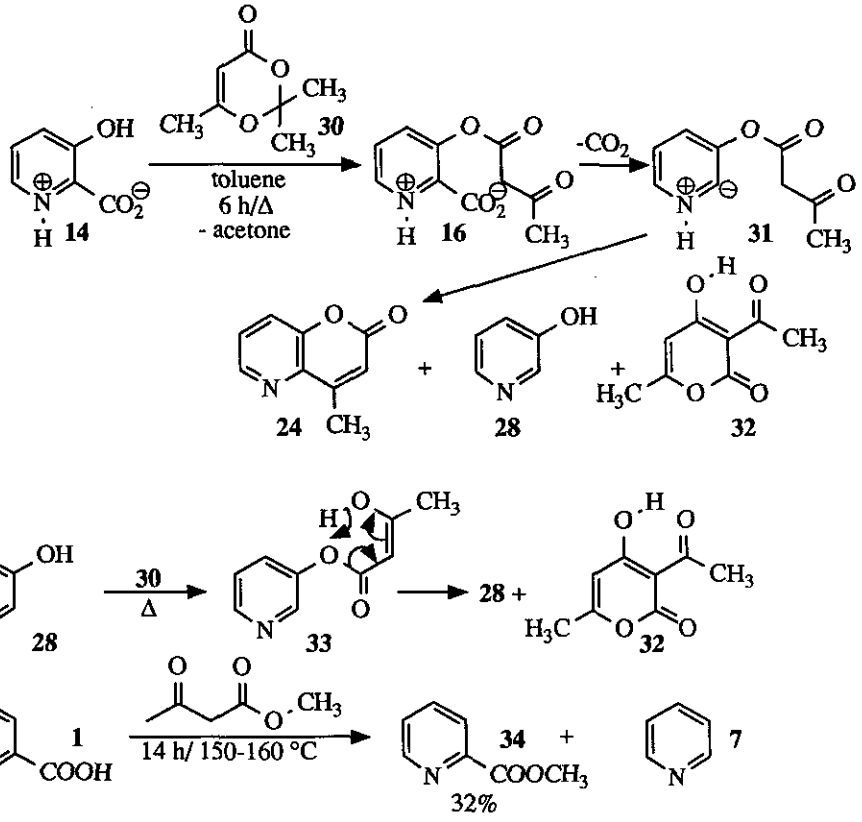
compounds we chose the commercially available 3-hydroxypicolinic acid (**14**) and the readily accessable 3-aminopicolinic acid (**15**).[7] These compounds were anticipated to form with diketene or the acetylketene precursor 2,2,4-trimethyl-1,3-dioxin-4-one (**30**) the corresponding *O*- or *N*-acetoacetylated intermediates (**16**) and (**17**). These compounds were expected to generate on heating the Hammick-intermediates (**18**) or (**19**) to give the final products (**24**) or (**25**) either *via* an 6-endo-trig cyclization **20** and subsequent elimination of H_2O (cf. **21**) or *via* an 6-exo-trig cyclization to **22** or **23** and subsequent elimination of H_2O. As side reaction the Hammick-intermediates (**18**) or (**19**) were anticipated to undergo proton-transfers such as depicted in **26** or **27** to afford the corresponding 3-hydroxy- or 3-aminopyridines (**28**) and (**29**) and diketene thus diminishing the yields of the desired Hammick-products (**24**) or (**25**).



A) REACTIONS OF 3-HYDROXYPICOLINIC ACID (**14**)

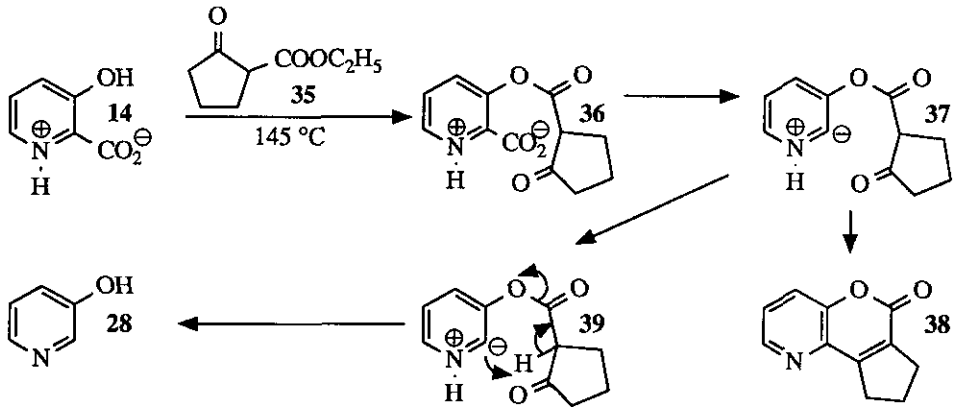
In the event heating of 3-hydroxypicolinic acid (**14**) with the acetylketene formed in situ from 2,2,6-tri-

methyl-1,3-dioxin-4-one (**30**) in boiling toluene for 6 h with simultaneous distillation of acetone gave the desired Hammick-cyclization product (**24**) albeit in only 25% yield as well as 74% of 3-hydroxypyridine (**28**) and dehydracetic acid (**32**). Variation of the experimental conditions e. g. heating of **14** with **30** in boiling xylene or heating of **14** with excess neat methyl or ethyl acetoacetate up to 180 °C did not raise the yield of **24** beyond 25%. Furthermore heating of **14** with **30** in DMSO to 160 °C furnished only 14% of **24**, whereas other polar solvents such as pyridine or DMF did not give any of the Hammick-product (**24**). All attempts, however, failed to isolate the anticipated *O*-acetoacetylated intermediate (**16**). Likewise, all model reactions of 3-hydroxypyridine (**28**) with 2,2,6-trimethyl-1,3-dioxin-4-one (**30**) or methyl or ethyl acetoacetate did not give any of the ester (**33**) since all these esters apparently decompose to 3-hydroxypyridine (**28**) and acetyl ketene, which dimerizes to dehydracetic acid (**32**).



To eliminate the possibility that the postulated Hammick-intermediate (**18**) (or the corresponding Hammick-intermediate with a free 3-hydroxy group) could react with methyl or ethyl acetoacetate in an intermolecular reaction to result finally in the same Hammick cyclization product (**24**), we heated picolinic acid (**1**) with

excess neat methyl acetoacetate and obtained only 32% of methyl picolinate (**34**) as well as pyridine (**7**). Furthermore, we were never able to isolate any trace of the cyclic hydroxy compound (**22**) as potential intermediate, which might either be due to the inherent instability of **22** under the employed reaction conditions or to the fact that the cyclization proceeds exclusively *via* the 6-endo-trig cyclization pathway depicted in **20**→**21**. Heating of 3-hydroxypicolinic acid (**14**) with neat excess ethyl 2-cyclopentanone carboxylate (**35**) to 145 °C afforded analogously *via* **36** and **37** the azacoumarine (**38**) in 25% yield as well as 3-hydroxypyridine (**28**). Again, the postulated intermediate (**36**) could not be isolated. The large amount of recovered 3-hydroxypyridine (**28**) is probably formed *via* **39**. The structures of the Hammick cyclization products (**24**) and (**40**) can be safely assigned based on the ir-carbonyl bands of **24** and **38**, which are typical for coumarines and quite different from the isomeric benzopyran-4-ones.

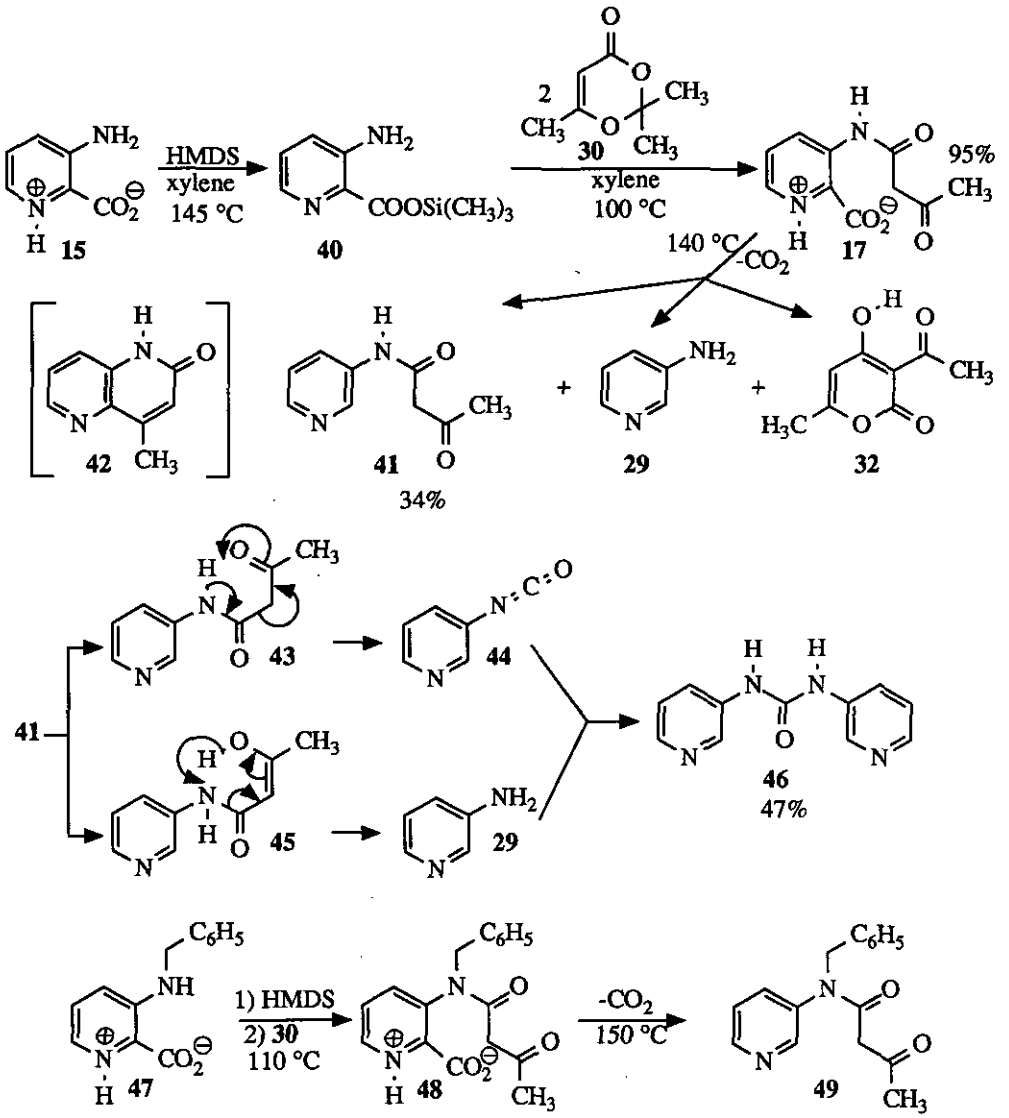


B) REACTIONS OF 3-AMINOPICOLINIC ACID (**15**)

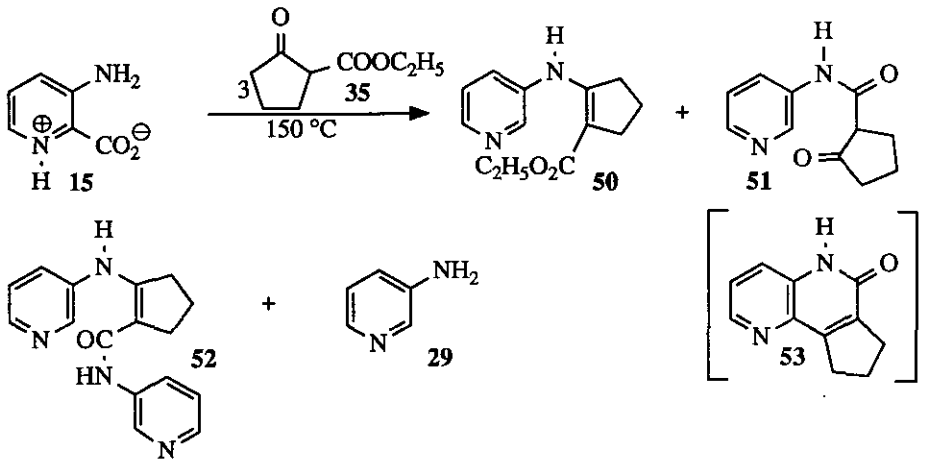
Due to the insolubility of 3-aminopicolinic acid (**15**) in unpolar solvents, **15** was silylated with hexamethyldisilazane (HMDS) in boiling xylene to **40** and then reacted with two equivalents of 2,2,6-trimethyl-1,3-dioxin-4-one (**30**) at 100 °C in xylene whereupon the crystalline acetoacetamide (**17**) could be isolated in 95% yield. Heating of (**17**) for 2 h at 140 °C gave after evaporation and chromatography 34% of the crystalline amide (**41**), which was also obtained in nearly quantitative yield on heating of 3-aminopyridine (**29**) with **30**, as well as 3-aminopyridine (**29**) and dehydracetic acid (**32**) but no trace of the desired Hammick cyclization product (**42**). Heating of **17** or of the amide (**41**) in mesitylene furnished probably *via* **43** and **45** the intermediates (**44**) and (**29**), which combine to give 47% of the *N,N'*-bis(3-pyridyl)urea (**46**) as well as 3-aminopyridine (**29**) and dehydracetic acid (**32**). For comparison purposes the urea (**46**) was synthesized by heating of

two equivalents of 3-aminopyridine (**29**) with urea.[8]

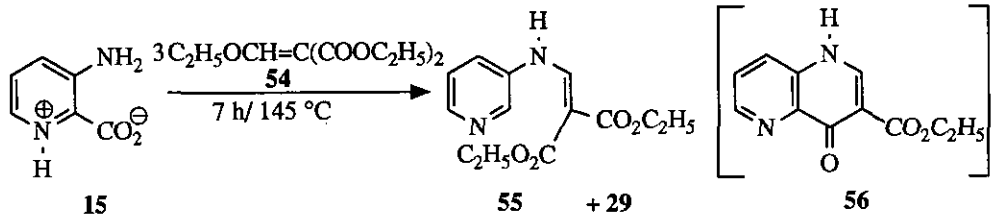
Since **17** contains an acidic amide-proton, which may contribute to the failure of the Hammick cyclization, we silylated the 3-*N*-benzylaminopicolinic acid (**47**), which is readily available *via* condensation of 3-amino-picolinic acid (**15**) with benzaldehyde followed by reduction with sodium cyanoborohydride, and converted the silyl compound with (**30**) to the *N*-acetoacetamide (**48**). Heating of **48** in mesitylene gave, however, only rise to the decarboxylated amide (**49**) and none of the desired Hammick cyclization product.

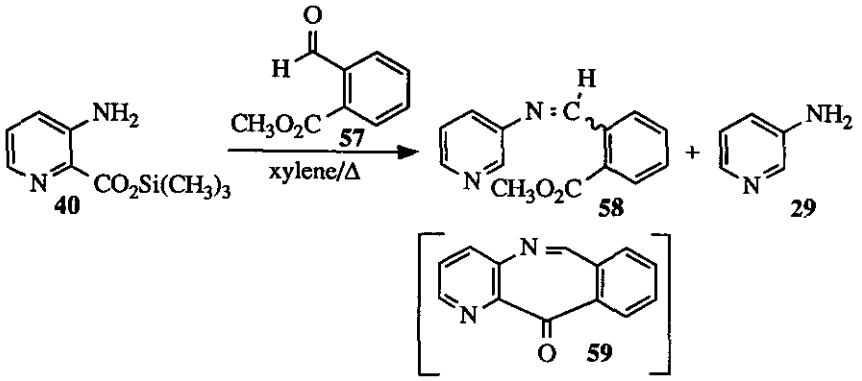


Heating of 3-aminopicolinic acid (**15**) with 3 equivalents of neat ethyl cyclopentanone-2-carboxylate (**35**) to 150 °C furnished mainly the enamino amide (**52**) besides the amide (**51**), the enamino ester (**50**) and 3-aminopyridine (**29**), but none of the desired cyclization product (**53**). At the present stage we cannot exclude, however, that the large part of the 3-aminopicolinic acid (**15**) decarboxylates to 3-aminopyridine (**29**) before condensation with ethyl cyclopentanone-2-carboxylate (**34**) (cf the subsequently described condensations of **15** with **54** and **57**). Reaction of **15** with ethyl cyclopentane-2-carboxylate (**35**) and DMAP[9] afforded selectively only the amide (**51**).



Likewise, heating of **15** with diethyl ethoxymethylenemalonate (**54**) at different temperatures furnished only the decarboxylated product (**55**), which is readily obtained by heating of 3-aminopyridine (**29**) with **54** in boiling ethanol, but no trace of the cyclization product (**56**).[10] **56** had previously been prepared in up to 80% yield by pyrolysis (Conrad-Limpach Reaction) of **55**.[10] Finally, heating of silylated 3-aminopicolinic acid (**40**) with methyl 2-formylbenzoate (**57**) in boiling xylene gave only in 50% yield the Schiff-base (**58**) as well as 49% of 3-aminopyridine (**29**) but no trace of the desired cyclization product (**59**).

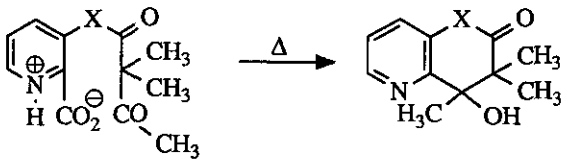




Since we suspect that the amino groups in free or silylated 3-aminopicolinic acid (**15**) or (**40**) are too basic to permit any Hammick cyclization, we anticipate that 3-acetylaminopicolinic acid[11] or 3-methanesulfonylaminopicolinic acid might react with excess 2,2,4-trimethyl-1,3-dioxin-6-one (**30**) or neat ethyl cyclopentane-2-carboxylate **35** to furnish the desired cyclization products corresponding to **42** and **53**.

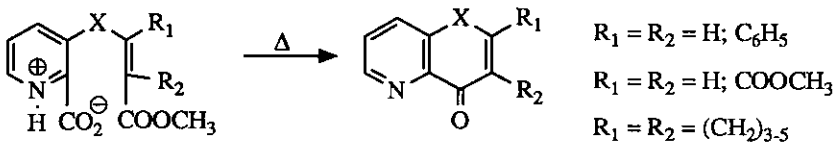
SUMMARY

Although it could be demonstrated that the intramolecular Hammick reaction (cyclization) is feasible, the hitherto achieved maximal yields of 25% are unattractive and disappointing. Since these low yields are at least partially due to the acidic methylene protons (cf. the postulated intermediates (**26**), (**27**) and (**39**)), acylated intermediates such as **60** or **61** (or the corresponding products derived from 2-methyl-2-alkoxycarbonylcyclopentanone) or intermediates such as **63** or **64**, which will not undergo intramolecular hydrogen transfer, will probably give much higher yields of the resulting cyclization products (**62**) or (**65**).



60 X = O
61 X = NR (R = Ac; SO_2CH_3)

62



63 X = O
64 X = NR (R = Ac; SO_2CH_3)

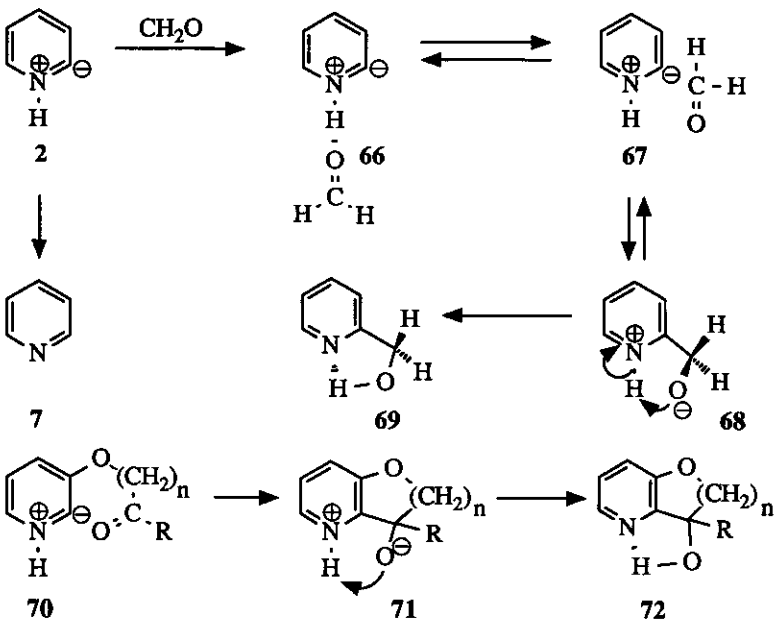
65

THEORETICAL STUDIES ON THE INTER- VERSUS THE INTRAMOLECULAR HAMMICK REACTION

Since the intramolecular Hammick reaction (cyclization) of 3-substituted picolinic acids afforded only moderate yields of the anticipated cyclization products, kinetic and enthalpic factors must be more important than the favorable entropy (cf. however the competing hydrogen shifts in **26**, **27** and **39**).

To get an insight into the factors which influence these Hammick cyclizations, semiempirical AM1-calculations were made of the reaction-profiles of inter- versus intramolecular Hammick reactions. For the intermolecular Hammick reaction the model reaction of the Hammick-intermediate (**2**) and formaldehyde was investigated. Due to strong ion dipole interaction, a well-defined orientation of the approaching formaldehyde could be found. The species (**66**) and (**67**) correspond to electrostatically bound ion dipole complexes being stabilized towards decomposition by about 9 kcal/mol, respectively. The species (**67**) "collapses" into the covalently bound ylid ion (**68**), which eventually gives rise to the formation of **69** *via* [1,4]H shift. The competing intramolecular formation of pyridine (**7**) from **2** *via* [1,2]H shift is, apart from being highly exothermic, associated with a fairly high barrier of 46.2 kcal/mol (compared to **68**) and, therefore, energetically not feasible.

In the intramolecular Hammick reaction (cyclization) there are analogous energetical barriers for the hydrogen shifts in **71**, indicating that the hydrogen shift **71**→**72** is the rate determining step rather than the bond formation (**67**→**68**). Furthermore, these calculations show a strong dependance of the activation energies of the rate determining hydrogenshifts in **71** to **72** on the ring size. The activation energy ΔE of the five membered transtion state (n=1) is much higher for **71** to **72** than for the corresponding six (n=2) and seven (n=3) membered transition states.



EXPERIMENTAL

For the column chromatography iron free SiO_2 60 (Merck, 0.040-0.063 mm) as well as Al_2O_3 (Woelm) (neutral or basic, A II or III) were used. The melting points were taken on a Kofler-melting point microscope and are not corrected.

4-Methyl-2*H*-pyrano[3,2-*b*]pyridine-2-one (**24**).

In a round bottom flask connected with a short Vigreux-column and distillation bridge a suspension of 0.70 g (5 mmol) of 3-hydroxypicolinic acid (**14**) was stirred in 20 ml of toluene at 120 °C (oil bath temperature) and 1.3 ml (10 mmol) of 2,2,6-trimethyl-1,3-dioxin-4-one (**30**) added gradually while distilling off the acetone. After 6 h no 3-hydroxypicolinic acid was anymore detectable on tlc. The toluene was evaporated and the dark residue was chromatographed in toluene-ethyl acetate (9:1) on a column of 50 g of SiO_2. Elution with this solvent mixture afforded 0.2 g (25%) of the azacoumarine (**24**). Further elution with 500 ml of toluene-ethyl acetate (2:1) gave 0.5 g (29.7%) of dehydracetic acid (**32**), whereas elution with 150 ml of ethyl acetate afforded 0.33 g (70%) of 3-hydroxypyridine (**28**). Filtration of the crude azacoumarine (**24**) in toluene over a column of 75 g neutral Al_2O_3 (A III) furnished colorless **24**, which was recrystallized from toluene-cyclohexane, mp 135 °C.

Replacement of toluene or xylene by pyridine, DMF, or addition of diisopropylethylamine did not give any azacoumarine (**24**). In DMSO at 160 °C only 10% of **24** were obtained.

Gradual heating of a mixture of 1.39 g (10 mmol) of 3-hydroxypicolinic acid (**14**) and 3.79 ml (30 mmol) of ethyl acetoacetate up to 180 °C and keeping the reaction mixture for 4 h at 180 °C with simultaneous removal of ethanol by slightly reduced pressure gave after concentration in vacuo and chromatography of the residue 23% of **24**. Likewise, silylation of 3-hydroxypicolinic acid (**14**) with a slight excess of hexamethyldisilazane (HMDS) and a trace of trimethylsilyl chloride in boiling xylene and subsequent reaction with excess ethyl acetoacetate did not raise the yield of **24**; ir ($CHCl_3$) 1730 (s), 1630 (w), 1590 (m), ^{1}H-nmr (300 MHz), $CDCl_3$) δ: 2.57 (3H, s), 6.54 (1H, s), 7.48 (1H, dd, J=6 and 8 Hz), 7.63 (1H, d, J=8 Hz), 8.6 (1H, d, J=6 Hz). Anal. Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.13; H, 4.39; N, 8.66.

Methyl picolinate (**34**).

A stirred suspension of 1.23 g (10 mmol) of picolinic acid (**1**) in 3.24 ml (30 mmol) of methyl acetoacetate was heated to 150 °C, whereupon a clear solution formed. After 14 h heating to 150-170 °C all **1** had disappeared according to tlc. After distillative removal of excess methyl acetoacetate in vacuo, the black residue (1.6 g) was chromatographed in toluene-ethyl acetate (2:1) on a column of 50 g SiO_2. Elution with 280 ml of toluene-ethyl acetate (2:1) furnished unreacted methyl acetoacetate. The subsequent 300 ml of solvent mixture eluted 0.5 g of crude methyl picolinate (**34**), which gave on distillation at 120 °C/26 mTorr 0.44 g (32%) of pure **34**, mp 41-43 °C (lit.,[12] 42-43 °C).

6,7,8,9-Tetrahydrocyclopenta [4,5]pyrano[3,2-*b*]pyridin-6-one (**38**).

A stirred suspension of 0.70 g (5 mmol) of 3-hydroxypicolinic acid (**14**) in 2.17 ml (15 mmol) of ethyl 2-cyclopentanonecarboxylate (**35**) was heated gradually to 160 °C, whereupon a dark homogeneous solution formed. After 6 h at 160 °C at slightly reduced pressure to remove the ethanol formed, 3-hydroxypicolinic acid (**14**) had disappeared according to tlc. The residual (3 g) were chromatographed in methyl *tert.*-butyl ether (MTB) on a column of 100 g SiO_2. The first 230 ml of MTB eluted the excess ethyl 2-cyclopentanonecarboxylate (**35**). The subsequent 200 ml of MTB afforded 0.235 g (25%) of the azacoumarine (**38**), which was recrystallized from cyclohexane to give the analytical sample mp 136-137 °C. Further elution with

900 ml of MTB furnished 0.35 g (74%) of 3-hydroxypyridine (**28**).

Analogous reaction of **14** with methyl 2-cyclopentanonecarboxylate gave about the same yield of **38**. Ir ($CHCl_3$) 3020 (w), 2980 (m) 1730 (s), 1630 (w), 1595 (w); ^{1}H-nmr ($CDCl_3$) δ: 2.19 (2H, q, J=7.5 Hz), 2.93 (2H, t, J=7.5 Hz), 3.22 (2H, t, J=7.5 Hz), 7.36 (1H, dd, J=6 and 8 Hz), 7.49 (1H, d, J=8 Hz), 8.52 (1H, d, J=6 Hz). Anal. Calcd for $C_{11}H_9NO_2$: C, 69.19; H, 4.94; N, 7.33. Found: C, 69.19; H, 4.97; N, 7.11.

3-(3-Oxobutylamido)picolinic acid (**17**).

A suspension of 2.07 g (15 mmol) of 3-aminopicolinic acid (**15**) was heated for 1.5 h with 3.13 ml of HMDS in 35 ml of abs. xylene, whereupon a clear solution formed of the trimethylsilyl ester of 3-aminopicolinic acid (**40**). **40** was treated for 48 h at 90-100 °C under slightly reduced pressure with 2.35 ml (18 mmol) of 2,2,6-trimethyl-1,3-dioxin-4-one (**30**) with simultaneous removal of acetone. During the reaction part of **17** started to crystallize. Concentration of the reaction mixture and filtration afforded 2.34 g of **17**, which was washed with a small amount of methanol. Concentration of the mother liquor furnished additional amounts of **17**, which was obtained in a combined yield of 3.16 g (95%), mp 178 °C (decomp.). Ir (KBr) 3410 (m broad), 3040 (m), 2920 (m), 1720 (s), 1690 (s), 1670 (s), 1600 (w), 1530 (s), 1470 (s); ^{1}H-nmr (300 MHz, DMSO-D_6) δ: 2.22 (3H, s), 3.71 (2H, s), 7.66 (1H, dd, J=6 and 8 Hz), 8.39 (1H, d, J=6 Hz), 8.78 (1H, d, J=8 Hz), 11.19 (s, 1H). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.22; H, 4.66; N, 12.48.

3-(3-Oxobutyrylamido)pyridine (**41**).

After heating a suspension of 0.69 g (5 mmol) of 3-aminopicolinic acid (**15**) and 1.2 ml (5.7 mmol) of HMDS in 25 ml of abs. xylene for 1.5 h at 135-140 °C, the clear, homogeneous solution of **40** was admixed with 0.65 ml (5 mmol) of 2,2,6-trimethyl-1,3-dioxin-4-one (**30**) and the reaction mixture was heated for 30 min at 140 °C at slightly diminished pressure. A second 0.65 ml (5 mmol) portion of **30** was added and heating at 140 °C continued for 2 h. After evaporation the dark reaction product (1.2 g) was chromatographed in ethyl acetate on a column of 50 g of SiO_2. The first 370 ml of ethyl acetate eluted dehydracetic acid (**32**) and other side products, whereas the subsequent 700 ml of ethyl acetate and ethyl acetate-methanol (9:1) furnished 0.3 g (34%) of the crystalline amide (**41**), mp 143 °C, on recrystallization from toluene. Ir ($CHCl_3$) 3300 (broad), 3030 (w), 3000 (m), 2960 (w), 1715 (s), 1685 (s), 1595 (m), 1540 (s), 1485 (m); ^{1}H-nmr (300 MHz, DMSO-D_6) δ: 2.24 (3H, s), 3.59 (2H, s), 7.33 (1H, dd, J=6 and 8 Hz), 8.03 (1H, d, J=8 Hz), 8.27 (1H, d,

J=6 Hz), 8.72 (1H, s), 10.18 (1H, s); ms (EI) m/z: 178 ($M^{\oplus}$-C_2H_3O), 121 ($M^{\oplus}$-CH_2COCH_3), 94 ($M^{\oplus}$-$C_4H_4O_2$) 85, 78, 67.

On heating a suspension of 0.94 g (10 mmol) of 3-aminopyridine (**29**) and 1.44 ml (11 mmol) of 2,2,6-trimethyl-1,3-dioxin-4-one (**30**) in 20 ml of abs. toluene for 2 h in an oil bath of 140 °C and simultaneous distillation of acetone and toluene, the crude product (1.85 g), obtained on evaporation, gave on filtration in ethyl acetate over a small column of SiO_2 and recrystallization from toluene 1.71 g (96%) of the amide (**41**).

1,3-Bis-(3-pyridyl)urea (**46**).

On heating 0.22 g (1 mmol) of 3-(3-oxobutyrylamido)picolinic acid (**17**) in 4 ml of mesitylene for 15 h at 160 °C and evaporation, the residue (0.2 g) was chromatographed on a column of 9 g SiO_2. Elution with 20 ml of ethyl acetate-methanol (95:5) removed impurities whereas the subsequent 60 ml of the same solvent mixture afforded 0.05 g (47%) of 3-aminopyridine (**29**). Continued elution with 120 ml of ethyl acetate-methanol (95:5) furnished 0.05 g (47%) of **46**, mp 217 °C (decomp.) (lit.,[13] 217 °C, decomp.).

On heating of 2 equivalents of 3-aminopyridine (**29**) with 1 equivalent of urea in xylene to 140 °C an authentic sample of **46** was obtained. Ms (EI) m/z: 213 ($M^{\oplus}$), 121 ($M^{\oplus}$-C_5H_4N-NH), 119, 94 ($M^{\oplus}$-C_5H_4N-NCO) 78, 67, 51.

3-Benzylaminopicolinic acid (**47**).

A suspension of 6.9 g (50 mmol) of 3-aminopicolinic acid (**15**), 10.43 ml (50 mmol) of HMDS and 5.59 ml (55 mmol) of freshly redistilled benzaldehyde in 150 ml of abs. xylene was heated for 6 h at 140 °C, whereupon initially a clear solution followed by a precipitate. After evaporation the yellowish crystalline precipitate was dissolved in 120 ml of methanol and reduced with gradually added portions of 3.3 g (50 mmol) of $Na[H_3BCN]$. After 15 h at 23 °C, addition of further 3.3 g (50 mmol) of $Na[H_3BCN]$ and stirring for 18 h at 24 °C, the methanol was evaporated and the residue was silylated with 10.43 ml (50 mmol) of HMDS in 200 ml abs. xylene for 3 h at 135 °C. After filtration with careful exclusion of humidity, the filtrate was evaporated and taken up in methanol, which was acidified with dilute HCl to pH = 6-6.2. After filtration of NaCl and evaporation the residue was recrystallized from methanol-H_2O to give pure **47**, mp 310-314 °C (decomp.). Ir (KBr) 3440 (w), 3280 (m), 3030 (w), 2920 (w), 2840 (w), 1600 (ss), 1575 (m), 1495 (ss), 1390 (s),

1220 (s); ^{1}H-nmr (300 MHz, DMSO-D_6) δ: 4.36 (2H, d, J=6 Hz), 6.68 (1H, d, J=8 Hz), 7.04 (1H, dd, J=6 and 8 Hz), 7.17-7.43 (5H, m), 7.68 (1H, d, J=6 Hz), 9.86 (NH, t, J=6 Hz); ms (EI) m/z: 228 ($M^{\oplus}$), 210 (M-H_2O), 181, 106, 91, 79, 78, 77, 65, 51.

3-(*N*-Benzyl-3-oxobutyrylamido)pyridine (**49**).

On heating of 3-benzylaminopicolinic acid (**47**) with excess 2,2,6-trimethyl-1,3-dioxin-5-one (**30**) in abs. xylene, evaporation and subsequent chromatography with ethyl acetate on silica gel only the crystalline amide (**49**), mp 157-158 °C, could be isolated.

Alternatively, reaction of 0.553 g (3 mmol) of 3-benzylaminopyridine with 0.59 ml (4.5 mmol) of 2,2,6-trimethyl-1,3-dioxin-5-one (**30**) for 18 h at 100 °C under slightly reduced pressure in 5 ml of abs. xylene afforded on evaporation and chromatography on silica gel with ethyl acetate 0.7 g (87%) of **49**, mp 157-158 °C. Ir ($CHCl_3$) 3070 (w), 3040 (m), 3000 (m), 2940 (w), 1725 (ss), 1660 (ss), 1605 (w), 1585 (m), 1480 (s), 1425 (s), 1395 (s), 1360 (s), 1275; ^{1}H-nmr (300 MHz, DMSO-D_6) δ: 2.04 (3H, s), 3.40 (2H, s), 4.94 (2H, s), 7.24-7.33 (5H, m), 7.39 (1H, m), 7.59 (1H, m), 8.33 (1H, s), 8.47 (1H, s); ms (EI) m/z: 268 ($M^{\oplus}$), 225 ($M^{\oplus}$-$COCH_3$) 183, 107, 91, 78, 65, 51.

2-Oxo-*N*-(3-pyridyl)cyclopentanecarboxamide (**51**), Ethyl 2-(3-pyridylamino)-1-cyclopentene-1-carboxylate (**50**) and *N*-(3-Pyridyl)-2-(3-pyridylamino)-1-carboxamide (**52**).

A stirred suspension of 0.41 g (3 mmol) of 3-aminopicolinic acid (**15**) in 1.3 ml (9 mmol) of ethyl cyclopentanonecarboxylate (**35**) was gradually heated under slightly reduced pressure to 150 °C and kept for 20 h at 150 °C. The dark residue (0.9 g) was chromatographed in ethyl acetate on a column of 40 g of SiO_2. The first 125 ml of ethyl acetate eluted excess ethyl cyclopentanonecarboxylate (**35**), whereas the subsequent 100 ml of ethyl acetate furnished 0.35 g (50%) of **50**. The final 400 ml of ethyl acetate gave 0.08 g (13%) of the amide (**51**). Elution with 600 ml of ethyl acetate-methanol (9:1) afforded 0.15 g (36%) of the enamino amide (**52**).

Heating of 0.28 g (3 mmol) of 3-aminopyridine (**29**) with 1.3 ml (9 mmol) of ethyl cyclopentanonecarboxylate (**35**) for 8 h to 140 °C and chromatography with ethyl acetate furnished 0.3 g (43%) of **51**, 0.08 g (13%) of **50** as well as 0.15 g (36%) of the enamino amide (**52**).

Reaction of 3-aminopicolinic acid (**15**) with ethyl cyclopentanonecarboxylate (**35**) in the presence of 0.05

equivalents of DMAP afforded exclusively the amide (**51**).

2-Oxo-*N*-(3-pyridyl)cyclopentane-1-carboxamide (**51**), mp 163-164 °C (from ethyl acetate/cyclohexane): ir ($CHCl_3$): 3320 (br), 300 (m), 2970 (s), 1730 (s), 1690 (ss), 1600 (s), 1535 (ss), 1485 (s); ^{1}H-nmr (300 MHz, DMSO-D_6) δ: 1.90-2.40 (7H, m), 7.32 (1H, dd, J=6 and 8 Hz), 8.28 (1H, d, J=8 Hz), 8.72 (1H, s), 9.96 (1H, s); ms (EI) m/z: 204 ($M^{\oplus}$), 149, 111, 94, 83, 67, 55.

Ethyl 2-(3-pyridylamino)-1-cyclopentene-1-carboxylate (**50**): ir ($CHCl_3$): 3280 (m, br), 3200 (w, br), 3030 (w), 2970 (m), 2820 (m), 1650 (ss), 1620 (ss), 1590 (s), 1575 (s), 1270 (ss); ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 1.33 (3H, t, J=7.5 Hz), 1.95 (2H, q J=7.5 Hz), 2.59 (2H, d, J=7.5 Hz), 2.83 (2H, t, J=7.5 Hz), 4.22 (2H, q, J=7.5 Hz), 7.22 (H, dd, J=6 and 8 Hz), 7.36 (1H, d, J=8 Hz), 8.28 (1H, d, J=6 Hz), 8.42 (1H, s), 9.63 (1H, s); ms (EI) m/z: 232 ($M^{\oplus}$), 186 ($M^{\oplus}$-EtOH), 157 ($M^{\oplus}$-CO_2Et), 130, 118, 104, 94, 78.

N-(3-Pyridyl)-2-(3-pyridylamino)-1-cyclopentene-1-carboxamide (**52**), mp 187-188 °C (from ethyl acetate/-cyclohexane): ir ($CHCl_3$) 3440 (m), 3260 (m, br), 3000 (m), 2970 (m), 2850 (m), 1640 (ss), 1590 (s), 1570 (s), 1520 (ss), 1480 (ss), 1410 (s), 1330 (s), 1265 (ss); ^{1}H-nmr (300 MHz; $CDCl_3$) δ: 1.95 (2H, d, J=7.5 Hz), 2.72 (2H, t, J=7.5 Hz), 2.87 (2H, t, J=7.5 Hz), 7.31 (2H, m), 7.54 (1H, d, J=8 Hz), 8.12 (1H, d, J=8 Hz), 8.23 (2H, m), 8.80 (1H, s), 8.87 (1H, s), 10.49 (1H, s); ms (EI) m/z: 280 ($M^{\oplus}$) 187 ($M^{\oplus}$-C_5H_4NNH), 160, 131, 94, 78, 67, 51.

Diethyl 2-(3-pyridylaminomethylene)malonate (**55**).

A stirred suspension of 0.41 g (3 mmol) of 3-aminopicolinic acid (**15**) in 0.61 ml (9 mmol) of diethyl ethoxymethylene malonate (**54**) was gradually heated to 140-150 °C and kept at this temperature for 12 h, whereupon everything passed into solution and the mixture turned dark. Evaporation of excess **54** in vacuo and chromatography of the residue on a column of 35 g SiO_2 with ethyl acetate furnished 0.5 g (63%) of diethyl 2-(3-pyridylaminomethylene)malonate (**55**). Recrystallization from ethyl acetate-cyclohexane gave pure **55**, mp 65-66 °C (lit.,[14]: 63-65 °C). Ir ($CHCl_3$) 3260 (w, br), 3200 (w, br), 3030 (w), 2990 (m), 1700 (s), 1660 (ss), 1620 (ss), 1590 (s), 1580 (s), 1410 (s), 1260 (ss); ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=7.5 Hz), 1.40 (3H, t, J=7.5 Hz), 4.28 (2H, q, J=7.5 Hz), 4.32 (2H, q, J=7.5 Hz), 7.35 (1H, dd, J=6 and 8 Hz), 7.50 (1H, d, J=8 Hz), 8.42 (1H, d, J=6 Hz), 8.51 (1H, s), 11.02 (1H, d, J=14 Hz); ms (EI) m/z: 264 ($M^{\oplus}$), 218 ($M^{\oplus}$-EtOH), 191 ($M^{\oplus}$-CO_2Et), 175, 162, 145, 118, 105, 94, 78, 65, 51.

Methyl-2(3-pyridyliminomethyl)benzoate (**58**).

Heating of 0.28 g (2 mmol) of 3-aminopicolinic acid (**15**) with 0.42 ml (2 mmol) of HMDS in 10 ml of abs. xylene for 1.5 h at 130 °C gave a clear solution of the silylated compound (**40**), which was than heated with 0.49 ml (3 mmol) of methyl 2-formylbenzoate (**57**) for 18 h at 140-145 °C. Chromatography in ethyl acetate on a column of 35 g of SiO_2 afforded 0.24 g (50%) of **58**, which was obtained pure on recrystallization from cyclohexane, mp 66-68 °C, as well as 0.23 g (49%) of 3-aminopyridine (**29**). **58**: ir ($CDCl_3$) 3000 (m), 2920 (m), 1720 (ss), 1625 (m), 1600 (m), 1270 (ss); ^{1}H-nmr (300 MHz, $CDCl_3$) δ: 3.96 (3H, s), 7.35 (1H, dd, J=6 and 8 Hz), 7.53-7.70 (3H, m), 8.02 (1H, d, J=8 Hz), 8.26 (1H, d, J=8 Hz), 8.56 (1H, s), 9.26 (1H, s).

REFERENCES

1) Part of the Ph. D. thesis of B. D. Bohn, Technische Universität Berlin, January 30, 1992. Part of this work was presented by H. V. at the International Congress on Heterocyclic Chemistry, August 11-16, 1991, Corvallis, Oregon, U.S.A.
2) B. R. Brown and D. Ll. Hammick, J. Chem. Soc., 1937,809 ; 1949, 173, 659.
3) B. R. Brown, D. Ll. Hammick, and D. Ll. Scholefield, J. Chem. Soc., 1950, 778 .
4) G. A. Karlivan and R. E. Valter, Khim. Geterots. Soedin, 1984, 1231.
5) For a review of the Hammick-reaction compare H. Vorbrüggen and M. Maas, Heterocycles, 1988, **27**, 2659.
6) F. Effenberger and J. König, Tetrahedron, 1988, **44**, 3281.
7) E. Sucharda, Ber., 1925, **58**, 1727.
8) a) L. Davis and H. W. Underwood, jr., J. Am. Chem. Soc., 1922, **44**, 2595.
   b) T. L. Davis and K. C. Blanchard, Org. Synthesis, Coll. Vol. I, 1941, 453.
9) D. F. Taber, J. C. Amedio, and Y. K. Patel, J. Org. Chem., 1985, **50**, 3618.
10) J. T. Adams, C. K. Bradsher, D. S. Breslow, S. T. Amore, and C. R. Hauser, J. Am. Chem. Soc., 1946, **68**, 1317.
11) Hoffmann La-Roche Inc., US Pat. 3415835 (Chem. Abstr. 1969, **70**, 57657).
12) C. Engler, Ber., 1894, **27**, 1784.
13) T. Curtius and E. Mohr, Ber., 1898, **31**, 2493-2495.
14) C. C. Price and R. M. Roberts, J. Am. Chem. Soc., 1946, **68**, 1204.

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