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Application of Organolithium and Related Reagents in Synthesis. Part 11[1]. Metallation of 2-Methyl- and 4-Methylnicotinic Acids. A Useful Method for Preparation of AZA-Isocoumarins

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APPLICATION OF ORGANOLITHIUM AND RELATED REAGENTS IN SYNTHESIS. PART 11[1]. METALLATION OF 2-METHYL- AND 4-METHYLNICOTINIC ACIDS. A USEFUL METHOD FOR PREPARATION OF AZA-ISOCOUMARINS

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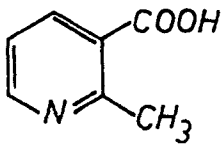
The metallation (LDA/THF) of 2-methyl- and 4-methylnicotinic acids (1) and (2), and the subsequent reaction of the lithiated species (3) and (4) with carbonyl electrophiles as a synthetic route of 5-aza- and 7-aza-isocoumarins (7), (8), (9) and (10), is described. The isocoumarins (9) and (10) appeared to be readily transformable into the corresponding naphthyridines (11) and (12).

The regiospecific introduction of C_1 units at various oxidation states by the aromatic directed metallation protocol[2] allows a subsequent chain extention and ring annelation to give systems that are not easily accessible by the classical methodology. The strongly acidifying effect of certain Z groups promotes facile deprotonation of an *ortho*-methyl group to form stable benzylic anions, that can undergo overall chain extention process. Such



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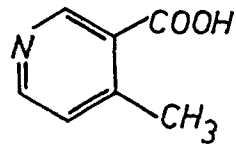

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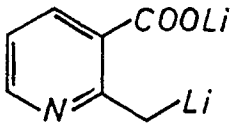

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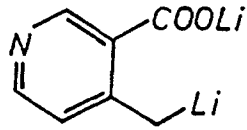

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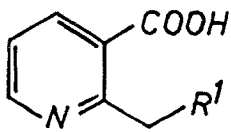

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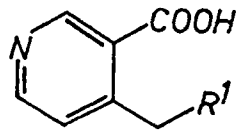


6

a, R^1 = $C(OH)(CH_2)_5$
b, R^1 = $CH(OH)C_6H_4OMe$-p
c, R^1 = COPh

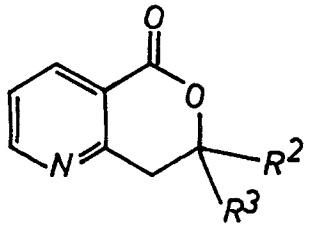
processes have been demonstrated for a number of directed metallation groups[3].

However, in the cases of the π-deficient heterocycles (e.g. pyridine) these processes and their exploitation in synthesis have been limited to the Z = -CN, -COOR[4,5]. We now report the advantage of the benzylic metallation strategy on *ortho*-methylnicotinic carboxylic acids (2- and 4-picolyl-lithiums) for the general synthesis of 5-aza- and 7-aza-isocoumarins including the 3-aryl-7-azaisocoumarin as the precursor for the preparation of *Alangium*[4] alkaloids skeleton system e.g. 2-(2'-hydroxyethyl)-3-phenyl-2,7-naphthyridin-1-one (**12**).

To this end, the reaction of the 2-methyl- (**1**) and 4-methylnicotinic (**2**) acids with lithium di-isopropylamide (LDA) has been examined.

The methyl-nicotinic acids (**1**) and (**2**) reacted in THF with 2.1 equivalents of LDA were efficiently converted into the corresponding bis-lithiated methylnicotinic acids (**3**) and (**4**), as it was demonstrated by the subsequent reactions with electrophiles. Treatment of the solutions of the lithiated species with a variety of carbonyl electrophiles (cyclohexanone, p-$MeOC_6H_4CHO$ and $C_6H_5CONMe_2$) furnished the desired products (**5**) and (**6**). The hydroxy products (**5a**), (**6a**), (**5b**) and (**6b**) without isolation on acid-driven cyclization yielded the corresponding aza-3,4-dihydro-isocoumarins (**7a**), (**8a**), (**7b**) and (**8b**). The benzoylated derivatives (**5c**) and (**6c**) upon treatment with acid (30% - H_2SO_4 at the room temperature) spontaneously cyclized into aza-isocoumarins (**9**) and (**10**).

The described methodology relating to the introduction of the alkyl substituent at the methyl group of the 2-methyl- and 4-methylnicotinic acids shows a considerable versatility for the selective synthesis of the 5-aza- and 7-aza-isocoumarins and related systems.



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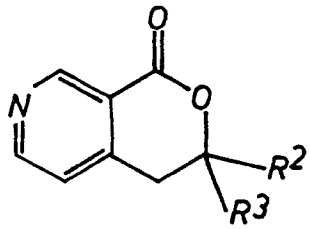

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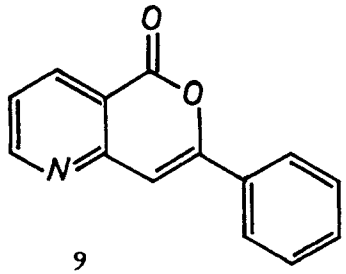
a, $R^2 = R^3 = (CH_2)_5$
b, $R^2 = H$; $R^3 = C_6H_4OMe\text{-}p$



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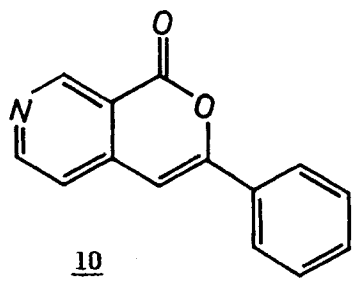

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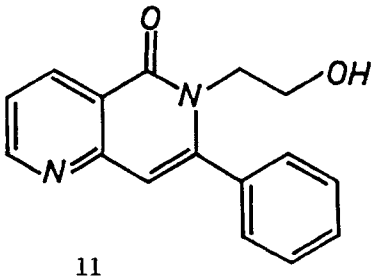

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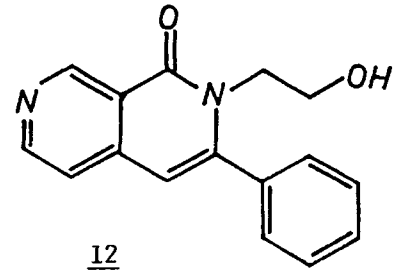

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Thus, the isocoumarins (**9**) and (**10**) upon reaction with ethanolamine in boiling methanol afforded the corresponding naphthyridin-ones (**11**) and (**12**).

Experimental

Melting points of the products were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra are of solution in $CHCl_3$ or KBr discs using a Zeiss-Jena Specord 71-IR. ^{1}H-NMR spectra were obtained with a Varian EM-360, or a Tesla BS-467 using Me_4Si as an internal standard. n-Butyllithium (nBuLi) was used without further purification. Di-isopropylamine was purified by the known method. Tetrahydrofuran (THF) was dried with calcium hydride and used directly after distillation under argon from sodium. Electrophiles were purified by standard methods before use.

2-Methylnicotinic acid (**1**); was prepared by the hydrolysis of 2-methylethylnicotinate (obtained as described[6] *via* condensation of acrolein with 3-aminoethylcrotonate) applying Baumgarten and Dornow[7] procedure. M.p. 209-211°C (lit.[7] m.p. 216-217°C). (Found: C, 61.3; H, 5.1; N, 10.0. Calc. for $C_7H_7NO_2$: C, 61.3; H, 5.1; N, 10.2%); IR (KBr) 1730 cm^{-1} (C=O); ^{1}H-NMR (CF_3COOH) 9.3 - 9.1 (1H, d, J 5Hz, 6-H), 8.9 - 8.6 (1H, m, 4-H), 8.3 - 7.8 (1H, m, 5-H), 3.2 (3H, s, Me-H).

4-Methylnicotinic acid (**2**); was prepared by the hydrolysis of 4-methyl-3-(4',4'-dimethyloxazolin-2'-yl)pyridine (obtained as described[8] *via* 1,4-addition of methyllithium to the 3-(4',4'-dimethyloxazolinyl-2'-yl)pyridine) applying Meyers and Gable[9] procedure. M.p. 205-206°C (lit.[9], m.p. 211-213°C). (Found: C, 61.4, H, 5.2, N, 9.8. Calc. for $C_7H_7NO_2$: C, 61.3, H, 5.1, N, 10.2%); IR (KBr) 1700 cm^{-1} (C=O); ^{1}H-NMR (CF_3COOH) 9.3 (1H, s, 1-H), 8.9 - 8.6 (1H, d, J 5Hz, 6-H), 8.1 - 7.9 (1H, d, J 5Hz, 5-H), 3.1 (3H, s, Me-H).

General Procedure for the Metallation - Electrophilic Substitution of the Methyl-nicotinic Acids (**1**) and (**2**)

To the methylnicotinic acid (**1**) or (**2**) (0.011 mol) in THF (75 ml) at -78°C LDA (0.024 mol) (prepared from a 1.4 M solution of nBuLi in hexane - 0.24 mol, and di-isopropylamine - 0.024 mol) in Et_2O (50 ml) was added dropwise, and the solution was held at -78°C for 0.5 h. The mixture was warmed up to 0°C for 0.5 h, and then recooled to -78°C. To the solution of the lithiated species at -78°C an electrophile: $C_6H_5CONMe_2$ (0.011 mol) or p-$MeOC_6H_4CHO$ (0.011 mol) or cyclohexanone (0.011 mol) in THF (50 ml), was added. The mixture after 0.5 h at -78°C was allowed to rise to the room temperature and it was stirred at this condition for 3 h, and then water (10 ml) was added. The reaction mixture after evaporation of the solvent gave an oily residue.

(a) p-Methoxybenzaldehyde or cyclohexanone as the electrophile.

The residue was acidified with 5% hydrochloric acid, and some amount of unreacted electrophile was extracted off with benzene. The acidic solution was left to stay for 7 days in the case of (**8b**) or 12 h in the case of (**7b**). Then it was adjusted to pH ~ 4 with K_2CO_3, and the white precipitate was filtered and purified by crystallization to give aza-3,4-dihydroisocoumarins (**7b**) or (**8b**). In the case of (**7a**) or (**8a**), the acidic solution was refluxed for 2 h. After adjusting to pH ~ 4 the brown oil was fallen out. It was extracted with CH_2Cl_2, and solidified after removing the solvent to give crude aza-3,4-dihydroisocoumarin (**7a**) or (**8a**), which was purified by crystallization.

(b) N,N-Dimethylbenzamide as the electrophile.

To the residue 30% - H_2SO_4 was added. The yellow solution was left to stay overnight at the room temperature, the white solid was filtered and crystallized from ethanol to give aza-isocoumarin (**9**) or (**10**).

The yields of the reactions, the physical properties, the IR and ^{1}H-NMR data, and analytical data are given below.

3,4-Dihydro-3-spirocyclohexane-5-azaisocoumrn (**7a**), (63%) m.p. 80-83°C (hexane); (Found: C, 71.8; H, 7.0; N, 6.3. Calc. for $C_{13}H_{15}NO_2$: C, 71.8; H, 6.9; N, 6.4%); IR (KBr) 1720 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.6 - 8.5 (1H, dd, J 1.5 and 5Hz, 6-H), 8.3 - 8.1 (1H, dd, J 1.5 and 7.5Hz, 8-H), 7.5 - 7.1 (1H, m, 7-H), 3.1 (2H, s, 4-CH_2-H), 2.0 - 1.0 (10H, m, CH_2-H).

3,4-Dihydro-3-spirocyclohexane-7-azaisocoumarin (**8a**), (58%) m.p. 85-88°C (hexane); (Found; C, 71.6; H, 7.0; N, 6.6. Calc. for $C_{13}H_{15}NO_2$: C, 71.8; H, 6.9; N, 6.4%); IR (KBr) 1715 cm^{-1} (C=O); ^{1}H-NMR (CF_3COOH) 9.6 (1H, br.s, 8-H), 9.2 - 9.0 (1H, d, J 5Hz, 6-H), 8.3 - 8.1 (1H, d, J 5Hz, 5-H), 3.5 (2H, s, 4-CH_2-H), 3.3 - 1.0 (10H, m, CH_2-H).

3,4-Dihydro-3-(p-methoxyphenyl)-5-azaisocoumarin (**7b**), (77%) m.p. 159-160.5°C (ethanol); (Found; C, 70.4, H, 5.3, N, 5.1. Calc. for $C_{15}H_{13}NO_2$: C, 70.6, H, 5.1, N, 5.4%); IR (KBr) 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.6 - 8.5 (1H, dd, J 1.5 and 5Hz, 6-H), 8.3 - 8.0 (1H, dd, J 1.5 and 8Hz, 8-H), 7.3 - 7.0 (3H, m, 7-H and Ar-H), 7.0 - 6.6 (2H, m, Ar-H), 5.6 - 5.3 (1H, m, CH-H), 3.6 (3H, s, OMe-H), 3.4 - 3.1 (2H, m, CH_2-H).

3,4-Dihydro-3-(p-methoxyphenyl)-7-azaisocoumarin (**8b**), (50%) m.p. 109-111°C (benzene - hexane = 1:1); (Found: C, 70.8; H, 5.3; N, 5.4. Calc. for $C_{15}H_{13}NO_2$: C, 70.6; H, 5.1; N, 5.1%); (KBr) 1700 cm^{-1} (C=O); ^{1}H-NMR (CF_3COOH) 9.6 (1H, s, 8-H), 9.2 - 9.0 (1H, d, J 5Hz, 6-H), 8.4 - 8.2 (1H, d, J 5Hz, 5-H), 7.7 - 7.6 (2H, d, J 8Hz, Ar-H), 7.3 - 7.1 (2H, d, J 8Hz, Ar-H), 4.1 (3H, s, OMe-H) 6.1 - 5.8 (1H, m, CH-H), 4.0 - 3.6 (2H, m, CH_2-H).

3-Phenyl-5-azaisocoumarin (**9**), (64%) m.p. 137-138°C (ethanol); (Found: C, 74.9; H, 4.2; N, 6.3. Calc. for $C_{14}H_9NO_2$: C, 75.3; H, 4.0; N, 6.3%); IR (KBr) 1740 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6) 9.0 - 8.8 (1H, dd, J1.5 and 5Hz, 6-H), 8.6 - 8.3 (1H, dd, J 1.5 and 7.5Hz, 8-H), 8.1 - 7.7 (2H, m, Ar-H), 7.7 - 7.4 (5H, m Ar-H).

3-Phenyl-7-azaisocoumarin (**10**),
(23%) m.p. 168-170°C (ethanol); (Found: C, 75.5; H, 4.0; N, 6.3. Calc. for $C_{14}H_9NO_2$: C, 75.3; H, 4.0; N, 6.3%); IR (KBr) 1725 cm^{-1} (C=O); ^{1}H-NMR ($CDCL_3$) 9.4 (1H, br.s, 8-H), 8.8 - 8.5 (1H, d, J 5Hz, 6-H), 7.9 - 7.6 (2H, m, Ar-H), 7.5 - 7.1 (4H, m, Ar-H), 6.8 (1H, s, 4-H).

Preparation of the Naphthyridines (**11**) and (**12**)

The aza-isocoumarin (**9**) or (**10**) (0.027 mol) and 2-aminoethanol (0.03 mol) in methanol (10 ml) was heated to reflux for 3 h in the case of (**9**) or 7 h in the case of (**10**), and left to stay overnight at the room temperature. The reaction mixture after evaporation of the solvent gave a solid residue. The residue was dissolved in 30% H_2SO_4. The solution was adjusted to pH ~ 4 with K_2CO_3. The crude product was then filtered and purified by crystallization.

The yields of the reactions, the physical properties, the IR and ^{1}H-NMR data, and the analytical data are given below.

2-(2'-Hydroxyethyl)-3-phenyl-1,2-dihydro-2,5-napthyridin-1-one (**11**),
(91%) m.p. 113-115°C (benzene - hexane = 1:1); (Found: C, 72.4; H, 5.5; N, 10.9. Calc. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.2; N, 10.5%); IR (KBr) 3440 cm^{-1} (O-H), 1660 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) 8.8 - 8.6 (1H, dd, J 1.5 and 5Hz, 6-H), 8.6 - 8.3 (1H, dd, J 1.5 and 7.5Hz, 8-H), 7.5 - 7.2 (6H, m, 7-H and Ar-H), 6.6 (1H, s, 4-H), 4.5 - 3.6 (5H, m, OH-H and CH_2-H).

2-(2'-Hydroxyethyl)-3-phenyl-1,2-dihydro-2,7-naphthyridin-1-one (**12**),
(82%) m.p. 227-229°C (ethanol); (Found: C, 72.5; H, 5.1, N, 11.0. Calc. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.2; N, 10.5%); IR (KBr) 3240 cm^{-1} (O-H), 1650 cm^{-1} (C=O); ^{1}H-NMR (CF_3COOH) 9.7 (1H, br.s, 8-H), 8.9 - 8.5 (1H, d, J 5Hz, 6-H), 8.2 - 7.8 (1H, d, J 5Hz, 5-H), 7.8 - 7.3 (5H, m, Ar-H), 6.9 (1H, s, 4-H), 4.8 - 4.2 (2H, m, CH_2-H), 4.1 - 3.8 (2H, m, CH_2-H).

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