PHOSPHORUS PENTOXIDE IN ORGANIC SYNTHESIS - PART 23[1]

SYNTHESIS OF 1,2,3,4-TETRAHYDRO-9-ACRIDINAMINES

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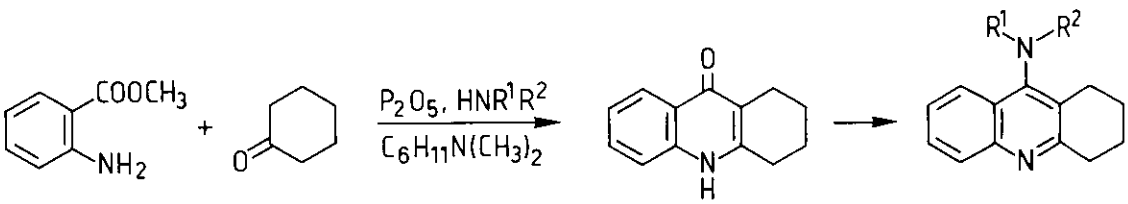
Abstract - 1,2,3,4-Tetrahydro-9(10H)-acridinone 2 was synthesized from methyl anthranilate and cyclohexanone using a mixture of P_2O_5 and N,N-dimethylcyclohexylamine as a condensing reagent. 1,2,3,4-Tetrahydro-9-acridinamines 3 were prepared, either directly from 2, using the new phosphoric amide reagents, or via the corresponding 9-chloro derivative 7 by reaction with amines.

Recently we reported that methyl anthranilate 1 reacts with cyclohexanone in a mixture of phosphorus pentoxide, N,N-dimethylcyclohexylamine and an aniline hydrochloride to give N-aryl-1,2,3,4-tetrahydro-9-acridinamines 3 in one pot[2].



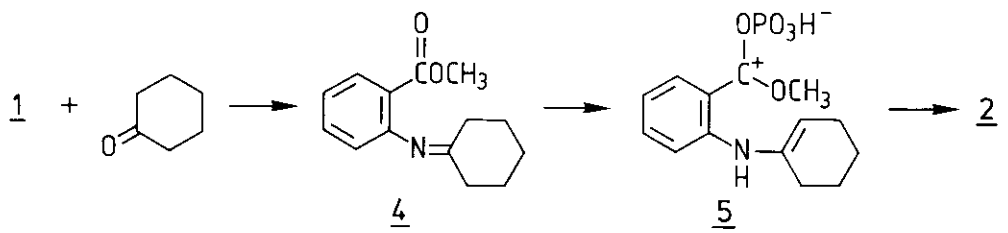
1 2 3

The compounds 3 have previously been prepared by a classical procedure implying the preparation of the corresponding oxo compound 2 followed by sequential reaction with $POCl_3$ and amines in the presence of phenol[3,4]. Related N-aryl-5,6,7,8-tetrahydro-4-quinolinamines show fungicidal activity against Phytophthora infestans, Plasmopara viticola and Erysiphe cirhoraceum[5]. It was therefore of interest to test the corresponding benzo-homologues 3 as fungicides. In order to optimize the biological activity through syntheses of suitable substituted 9-anilino-tetrahydroacridines 3 it was decided to follow the procedure of Topliss and Martin[6]. This

method is based on an operational scheme for the stepwise selection of new analogs of an active lead compound (3: R_1 = H, R_2 = C_6H_5). For this purpose we needed a series of 9-mono- and dichloro- and methyl-anilinotetrahydroacridines 3. Unfortunately, the one pot synthesis of 3 from methyl anthranilate (1) did not result in high yields, when the reagent mixtures were prepared from chloroanilines. In the present investigation the procedure was therefore modified, and the intermediate oxo compound 2 was used as a starting material.

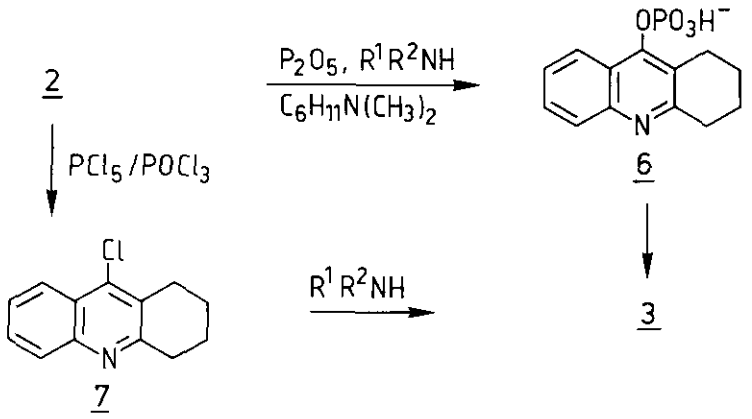
RESULTS AND DISCUSSION

The tetrahydroacridinone 2 was prepared in 50% yield by heating a mixture of 1, cyclohexanone, phosphorus pentoxide, and N,N-dimethylcyclohexylamine at 170 - 210°C. The reaction conditions were identical to those reported for preparations of tetrahydroacridines 3[2], except that no anilines were added to the reaction mixtures. Therefore, the reaction could not proceed further than to the stage of tetrahydroacridinone 2. It is believed that methyl anthranilate 1 condenses with cyclohexanone producing an intermediate 4, which is phosphorylated at the carbonyl oxygen atom of the ester group to give the reactive intermediate 5 which easily undergoes an intramolecular enamine acylation.



The reaction proceeded in two exothermic steps. When the mixture reached 150°C, a weak exothermic reaction was registered accompanied by a colour change to yellow. At 160°C a second strong exothermic reaction took place, and the temperature increased to 215°C. The colour changed to brown. Yield optimisation was only performed to the extent of getting a reaction mixture easy to handle. If P_2O_5 and N,N-dimethylcyclohexylamine alone was heated to the desired temperature of 210°C and if a mixture of cyclohexanone and methyl anthranilate was added later, big, hard lumps were formed, which made mechanical stirring almost impossible. Easy to

handle conditions were received, when all the reagents were mixed at room temperature in the molar ratio P_2O_5 : DMCA : cyclohexanone : methyl anthranilate equal to 1 : 1 : 0.6 : 0.5, followed by heating on an oil bath. In all cases a yield around 50% was obtained, and 2 could be isolated easily by filtration of the alkaline hydrolysate from the reaction mixture.



The tetrahydroacridines 3 were obtained according to the procedure of Pedersen and Carlsen[7] by reaction of 2 with a mixture of phosphorus pentoxide, an aniline hydrochloride and N,N-dimethylcyclohexylamine at 200°C. It is believed that this reaction mixture can produce a methaphosphate ion intermediate, which reacts with the enol form of 2 to give 6. The phosphate group of 6 is a good leaving group in the subsequent nucleophilic aromatic substitution reaction, which produces 3 (Table 1). The chloroacridine 7 may also be an intermediate, because chlorine anions, present in the reaction mixture, can compete with deactivated anilines in the nucleophilic substitution of the acridinyl phosphate 6. A proof of this pathway is the detection of 7 in low concentration by TLC at the beginning of the reactions, particularly when anilines with low nucleophilicity were used. With the sterically hindered and less nucleophilic 2,6-dichloroaniline as a reaction partner, the chloro compound 7 was isolated in 38% yield, whereas the corresponding anilinoacridine 3h could not be detected. This is the first example of a substitution of chlorine for an enol oxygen by the use of phosphorus pentoxide mixed with an amine hydrochloride.

Table 1: Preparation of tetrahydroacridines 3.

3	R^1	R^2	2 → 3 [%] (Reaction Time and Temp.)	7 → 3 [%] (Reaction Time and Temp.)	Mp [°C] (Solvent)	Lit.mp [°C]
a	H	C_6H_5	80 (4h, 200°C)		238-239.5 (MeOH)	235-236[8]
b	H	2-ClC_6H_4	51 (5h, 200°C)		174-175 (Ligroin 100-140°C)	175-177[8]
c	H	3-ClC_6H_4	59 (3h, 200°C)		155.5-156 (AcOEt)	156[8]
d	H	4-ClC_6H_4	31 (20h, 180°C)		157-159 (AcOEt)	162[8]
e	H	2,3-$Cl_2C_6H_3$	55 (3h, 200°C)		179-181 (AcOEt)	
f	H	2,4-$Cl_2C_6H_3$	38 (3h, 200°C)		184-185 (AcOEt)	
g	H	2,5-$Cl_2C_6H_3$	32 (3h, 200°C)		152-153	
h	H	2,6-$Cl_2C_6H_3$	0	0	68-72	
i	H	3,4-$Cl_2C_6H_3$	82 (3h, 200°C)		173-174 $(isoPr)_2O$	
j	H	3,5-$Cl_2C_6H_3$		80 (3h, 210°C)	161-162	
k	H	2,6-$(CH_3)_2C_6H_3$	33 (5h, 200°C)		123-125	
l	H	2-pyridyl		33 (3h, 190°C)	206-209	
m	H	Cyclohexyl	0	59 (24h, 135°C)	73-77	
n	N=CH-N=CH			48 (30min, 165°C)	185.5-186.0	

Table 2: ^{1}H-NMR and microanalysis.

3	^{1}H-NMR [ppm]	Found/Calcd.			
		C	H	N	Cl
a	δ($CDCl_3$/CF_3COOH) - 1.9(4H,m);2.7(2H,t); 3.3(2H,t);6.3-8.1(9H,m)				
b	δ($CDCl_3$) - 1.9(4H,m);2.7(2H,t);3.2(2H,t); 6.1-8.1(8H,m)				
c	δ($CDCl_3$) - 1.9(4H,m);2.7(2H,t);3.1(2H,t); 5.9(1H,s,NH);6.4-8.1(8H,m)				
d	δ($CDCl_3$) - 1.9(4H,m);2.7(2H,t);3.2(2H,t) 5.8(1H,s);6.4-8.1(8H,m)				
e	δ($CDCl_3$) - 1.9(4H,m);2.8(2H,t);3.2(2H,t); 8.2(8H,m)	66.4 66.5	4.8 4.7	8.1 8.2	20.7 20.7
f	δ($CDCl_3$) - 1.9(4H,m);2.7(2H,t);3.2(2H,t); 6.1(1H,s,NH);6.1-8.1(7H,m)	66.1 66.5	4.4 4.7	7.9 8.2	20.6 20.7
g	δ($CDCl_3$) - 1.9(4H,m);2.7(2H,t);3.2(2H,t); 6.1-8.1(8H,m)	66.1 65.5	4.7 4.7	8.1 8.2	20.8 20.7
h	δ($CDCl_3$) - 1.8(4H,m);2.4(2H,t);3.1(2H,t); 5.8(1H,s,NH);6.7-8.1(7H,m)	66.5 66.5	4.9 4.7	8.5 8.2	20.4 20.7
i	δ($CDCl_3$) - 1.9(4H,m);2.7(2H,t);3.1(2H,t); 6.0(1H,s,NH);6.3-8.1(7H,m)	66.5 66.5	4.7 4.7	8.2 8.2	20.7 20.7
j	δ($CDCl_3$) - 1.9(4H,m);2.6(2H,t);3.2(2H,t); 6.0(1H,s,NH);6.8-8.1(7H,m)	66.9 66.5	5.0 4.7	8.3 8.2	20.4 20.7
k	δ($CDCl_3$) - 1.9(4H,m);2.1(6H,s);2.5(2H,t); 3.1(2H,t);5.8(1H,s,NH);7.1-8.0(7H,m)	82.7 83.4	7.0 7.3	9.1 9.3	
l	δ($CDCl_3$/CF_3COOH) - 1.9(4H,m);2.7(2H,t);3.3 (2H,t);6.9-8.3(9H,m)	79.0 78.5	6.3 6.2	14.7 15.2	
m	δ($CDCl_3$) - 1.0-2.1(14H,m);2.7(2H,t);3.1 (2H,t);3.6(1H,m);7.2-8.1(4H,m)	81.0 81.4	8.8 8.6	10.0 10.0	
n	δ($CDCl_3$) - 1.9(4H,m);2.7(2H,t);3.2(2H,t); 7.1-8.2(4H,m);8.4(2H,s)	72.1 72.0	5.8 5.6	22.4 22.4	

For comparison we made a few tetrahydroacridines 3 in the classical way via 7 with amines in the presence of catalytic amounts of NH_4Cl at elevated temperature. This procedure did not lead to improved overall yields as compared with the one pot reaction. However, the classical procedure 2 → 7 → 3 is more generally applicable. This was clearly demonstrated in the reactions involving cyclohexylamine, where 3 could be prepared only via 7. However, the latter procedure could not be used for reaction of 7 with 2,6-dichloroaniline. When DMF was used as a solvent, the only isolated product was 9-dimethylamino-1,2,3,4-tetrahydroacridine. 3h was obtained by melting a mixture of 7 and the sodium salt of 2,6-dichloroaniline.

FUNGICIDAL ACTIVITY

The screening against powdery mildew (Erysiphe graminis) on barley was performed as described in the patent literature[9]. The minimum inhibiting concentrations for 95% control 'in vivo' of the active compounds are summarized in Table 3. Compound 3a, the lead compound, has shown the highest activity.

Compounds 3b, 3d, 3e, 3g-i, 3k-n, and 3(R^1=H;R^2=4-F-C_6H_4), 3(R^1=H;R^2=3-CH_3-C_6H_4), 3(R^1=H; R^2=4-CH_3-C_6H_4) and 3 (R^1=H;R^2=4-C_2H_5-C_6H_4) were not inhibitory at 200 ppm.

Substituents of the aniline moiety of 3 with +I and +M as well as -I and -M effects decreased the control of the fungus.

Table 3: Fungicidal Activities of Tetrahydroacridines 3

Compound	R^1 = H R^2	Erysiphe graminis on barley Minimum inhibitory concentration
3a	C_6H_5	20 ppm
3c	3-Cl-C_6H_4	200 ppm
3f	2',4-Cl_2-C_6H_3	200 ppm
3j	3,5-Cl_2-C_6H_3	200 ppm

1,2,3,4-Tetrahydro-9(10H)-acridinone (2).

P_2O_5 (0.2 mol), N,N-dimethylcyclohexylamine (0.2 mol), cyclohexanone (0.12 mol) and methyl anthranilate (0.1 mol) were mixed at room temperature and placed in an oil bath preheated to 170°C. When the exothermic reaction ceased, the mixture was heated with stirring at 210°C for 4 h. The mixture was allowed to cool to 130°C and was subsequently hydrolyzed with water. 2M NaOH was added until pH 10 and 2 precipitated as a yellow powder which was isolated by filtration and washed with ethanol and ether. The crude product was recrystallized from EtOH to give 2 in 50% yield.

9-Chloro-1,2,3,4-tetrahydroacridine (7) was prepared from 2 using $POCl_3$ and PCl_5 according to the procedure of Braun et al.[10]

Preparation of 1,2,3,4-tetrahydroacridines 3 starting from 2.

General procedure:

P_2O_5 (0.2 mol), N,N-dimethylcyclohexylamine (0.2 mol) and an aniline hydrochloride (0.2 mol) were mixed at room temperature and heated with stirring at 200°C in an oil bath until a homogeneous mixture was obtained. 2 (0.05 mol) was added and the reaction mixture was heated at 180-200°C for 3-20 h (Table 1). When cooled to about 130°C, the mixture was hydrolyzed by addition of water and subsequent addition of 2 M NaOH until pH 11. The water phase was extracted with ether or CH_2Cl_2. The crude products were subjected to silica chromatography as follows (compound, solvent for eluation): 3d, AcOEt; 3e, AcOEt; 3f, AcOEt; 3g, 2.5% MeOH in CH_2Cl_2; 3i, ether; 3k, acetone. In all other cases pure material was obtained directly by recrystallization of the crude products.

Preparation of 1,2,3,4-tetrahydroacridines 3 starting from 7.

General procedure:

7 (0.03 mol) was heated with an amine (0.04 - 0.25 mol) and catalytic amounts of NH_4Cl at 135 - 210°C for 0.5-24 h (Table 1). The cooled reaction mixture was dissolved in CH_2Cl_2, washed with 2M NaOH and subjected to silica chromatography as follows (compound, solvent for eluation): 3j, ether; 3l, AcOEt; 3m, 15% MeOH in CH_2Cl_2; 3n, 10% 2-propanol in $CHCl_3$.

9-(2,6-Dichloroanilino)-1,2,3,4-tetrahydroacridine (3h).

2,6-Dichloroaniline (0.6 mol) was dissolved in THF and NaH (0.3 mol) was added. When evolution of hydrogen had ceased, 7 (0.015 mol) was added. THF was distilled off at atmospheric pressure and the remaining mixture was heated under N_2 at 160°C for 6 h. The cooled reaction mixture was dissolved in CH_2Cl_2, washed with 2M NaOH and chromatographied on silica with AcOEt to give an impure oil which was triturated with MeOH.

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Received, 14th January, 1985