

SYNTHESIS OF 5H-DIPYRIDO[1,2-a:3',2'-e]PYRIMIDIN-5-ONE AND 5H-PYRIDO-[3',2':5,6]PYRIMIDO[1,2-a]QUINAZOLIN-5-ONES

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Abstract - α -Amino-N-heteroarenes on cyclocondensation with 2-chloropyridine-3-carboxylic acid chloride afford the title compounds 4 and 7. Although compound 4 is obtained in one-pot while compound 7 is formed via its amide intermediate 6.

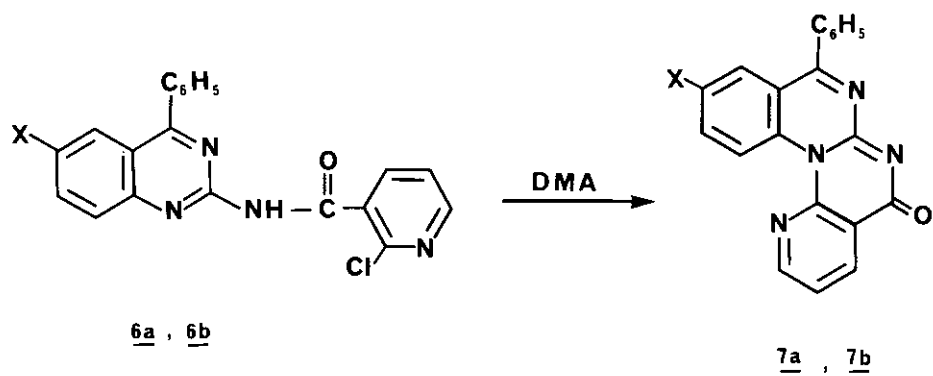
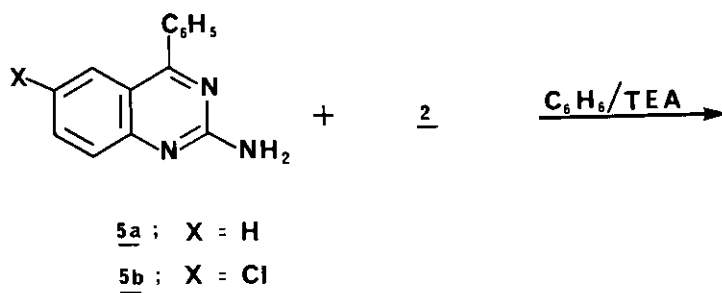
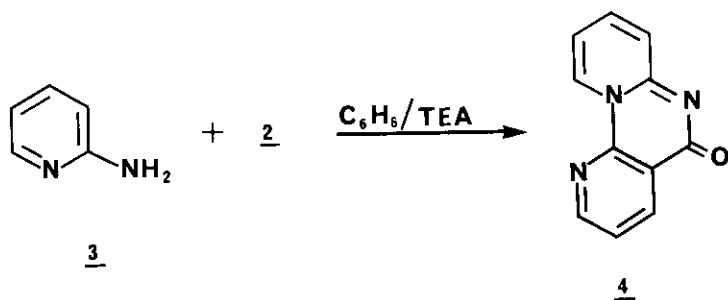
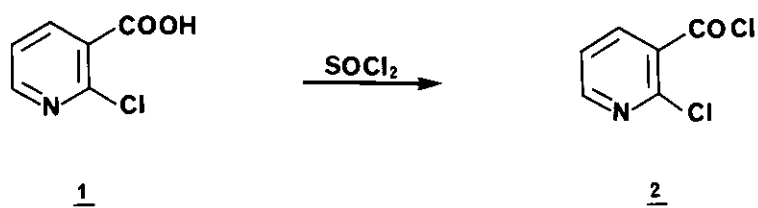
As a part of an ongoing research programme on the synthesis of novel heterocyclic compounds in search of interesting biological properties, we have earlier reported on the synthesis and biological activity of quinazolino[3,2-a]quinazolinones¹ and quinazolino[3,2-b][1,2,4]benzothiadiazine dioxides². In continuation of these efforts, we synthesized dipyridopyrimidinone 4 and pyridopyrimidoquinazolines 7, although pyridopyrimidones³ and quinazolinones⁴ have been studied extensively in the chemical literature but the title ring system 7 has not been previously reported. Therefore, herein we describe a facile synthesis for this class of heterocyclic compounds.

Reaction of 2-chloropyridine-3-carboxylic acid 1 via its acid chloride 2 with 2-aminopyridine 3 in benzene and triethylamine afforded 5H-dipyrido[1,2-a:3',2'-e]pyrimidin-5-one 4 in 42% yield, mp 218-220°C; IR (KBr): 1620, 1605 cm⁻¹; MS, m/z 197 (M⁺), 169 (M-CO)⁺, 155 (M-NCO)⁺. In this reaction, it is observed that intermediate amide could not be isolated.

In literature⁵ compound 4 was prepared by the reaction of 1 with 3 via the intermediate, N-(2-pyridyl)-amide followed by saponification. Hence, the present method offers a one-pot synthesis for compound 4.

Extending this reaction to 2-aminoquinazolines i.e., the reaction of 2-chloropyridine-3-carbonyl chloride 2 with 2-amino-4-phenyl-2(1H)-quinazoline 5a in benzene and triethylamine gave N-(4-phenylquinazolin-2-yl)-2-chloropyridine-3-carboxamide 6a, mp 175-178°C, in 75% yield; IR (KBr): 3055, 1670 cm⁻¹; MS, m/z 340 (M⁺). Similarly, 2-amino-5-chloro-4-phenyl-2(1H)-quinazoline 5b gave the corresponding carboxamide 6b, mp 186-188°C, in 82% yield; IR (KBr): 3050, 1665 cm⁻¹; MS, m/z 395 (M⁺).

The quinazoline carboxamides 6a and 6b were later cyclized by refluxing in dimethyl acetamide (DMA) for 20 h to obtain 8-phenyl-5H-pyrido[3',2':5,6]pyrimido[1,2-a]quinazolin-5-ones 7a and 7b in 55% and 68% yields, respectively.



7a: mp 276-280°C (decomp.); IR (KBr): 1620, 1590 cm^{-1} ; MS, m/z 325 (M^+), 324 (M-H^+), 7b: mp 298-300°C (decomp.); IR (KBr): 1625, 1590 cm^{-1} , MS, m/z 360 (M^+), 359 (M-H^+).

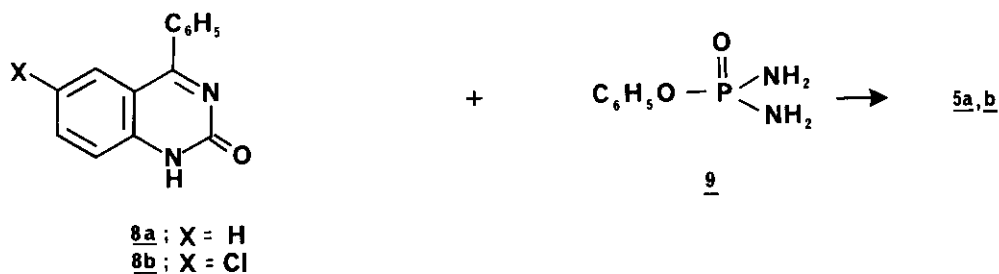
The observation of the direct cyclization and the non-isolation of the intermediate amide in the case of reaction of 2-aminopyridine with 2 is explained on account of the high degree of basicity of 2-aminopyridine compared to 2-amino-4-phenyl-2(1H)-quinazoline.

In a typical experiment, 2-chloropyridine-3-carboxylic acid 1 (1 mmol) and thionyl chloride (6 ml) were refluxed for 4 h. The excess of thionyl chloride was distilled off, benzene (10 ml) was added and was also distilled off, so as to remove the traces of thionyl chloride. The 2-chloropyridine-3-carbonyl chloride thus formed was taken in benzene (40 ml) and added, while stirring to a mixture of 2-aminopyridine 3 (1 mmol) or 2-amino-4-phenyl-2(1H)-quinazoline 5 (1 mmol) and triethylamine (1 mmol) taken in benzene (30 ml). On completion of the addition, the reaction mixture was refluxed for 4 h and cooled. The solid separated was filtered and from the filtrate, benzene was removed under reduced pressure to yield the crude products 4 and 6.

Compound 4 was purified by subjecting it to column chromatography on silica gel using chloroform: methanol (9.7:0.3) as eluent, whereas 6 was purified by recrystallization from methanol.

The N-substituted 2-chloropyridine-3-carboxamide 6 (0.5 mmol) was dissolved in DMA (5 ml) and refluxed for 20 h. The reaction mixture was poured in ice cold water. The solid separated was dried and recrystallized from methanol to yield 7.

2-Amino-4-phenyl-2(1H)-quinazolines 5 required as starting materials were prepared from 4-phenyl-2(1H)-quinazolines⁶ 8 employing phenyl phosphorodiimide (PPDA)⁷ 9 in one step, although in the literature compounds 5 had been prepared by the amination of 2-chloro-4-phenyl-2(1H)-quinazolines in ethanolic ammonia under pressure.



In a general procedure, a mixture of 4-phenyl-2(1H)-quinazoline 8a (1 mmol), PPDA 9 (1.8 mmol) and diphenyl ether (60 ml) was heated for 3 h at 250°C. The mixture on cooling was filtered and the filtrate was diluted with dichloromethane (75 ml). Dry hydrogen chloride gas was passed into the dichloromethane

solution to precipitate the hydrochloride of 2-amino-4-phenyl-2(1H)-quinazoline as a solid. This on treatment with 10% sodium hydroxide solution liberated the base 5a in 60% yield, mp 171-172°C (Lit.⁸, mp 169-170°C). 5b: mp 176-177°C in 63% yield. Satisfactory elemental analyses for C, H and N were obtained for all new compounds.

REFERENCES AND NOTES

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8. The IR spectrum of compound 5 was superimposable to the compound synthesized by the literature method: M.L. Hoefle and H. Holmes, U.S. Patent, 3,305,553 (1967); C.A., 66, 115730t (1967).

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