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2-ARYL-OXAZOLO- AND THIAZOLOPYRIDINES. SYNTHESIS VIA CYCLIZATION OF N-(2-CHLORO-3-PYRIDINYL)ARYLAMIDES AND THIOAMIDES

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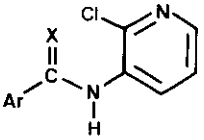
Abstract - Chloropyridinylenamides can be easily converted into oxazolo- and thiazolo [5,4-b]pyridines by treatment with polyphosphoric acid and Lawesson reagent respectively.

Oxazolo- and thiazolopyridines are a class of condensed heterocyclic compounds which are interesting owing to their analgesic, antipyretic and antiinflammatory properties[1]. Such compounds and particularly the 2-aryl derivatives can be prepared by only a few methods, mainly by reacting aminohydroxy- and aminomercaptopyridines with aromatic acids or anhydrides[1].

We wish to report in this paper a novel and convenient method for the preparation of oxazolo- and thiazolo [5,4-b]pyridines from N-(2-chloro-3-pyridinyl)arylamides (1) :

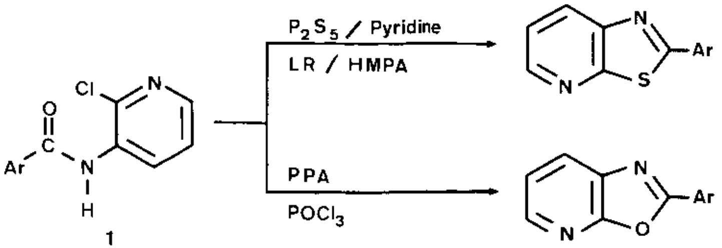


1 X = O

2 X = S

These compounds (1) are readily accessible via Schotten-Baumann reaction between 2-chloro 3-aminopyridine and an appropriate acid chloride.

Treatment of arylamides (1) by a sulfurating agent does not lead to the corresponding thioamides (2) but gives spontaneously the 2-arylthiazolo[5,4-b]pyridines (3) (scheme I) :



1

3

4

Scheme I

This cyclization reaction can be effected by using phosphorus pentasulfide in pyridine but the best sulfurating agent with respect to the ease of manipulation and overall yields is undoubtedly the dimer of p-methoxyphenylthionophosphine sulfide, commonly called Lawesson reagent (LR)[2].

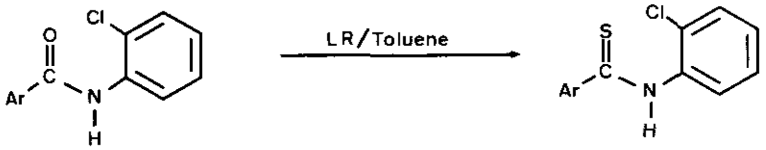
As a result of the considerable reactivity of the chloride functionality at α position to the nitrogen atom in the pyridine ring[3], these reactions have an extensive generality. Thus treatment of arylamides (1) with polyphosphoric acid, phosphorus pentoxide or phosphoryl chloride gives rise to the corresponding oxo derivatives, 2-aryl-oxazolo[5,4-b]pyridines (4) (scheme I). The results are summarized in Table I[4] :

Ar	Amide (1)	Thiazolopyridine (3) (LR)		Oxazolopyridine (4) (PPA)	
Phenyl	1a m.p. 89-90°C	3a m.p. 121°C	(41%)	4a m.p. 99°C	(45%)
4-Chlorophényl	1b m.p. 145-6° C	3b m.p. 170-1°C	(36%)	4b m.p. 153-4°C	(38%)
2-Furyl	1c m.p. 100-1° C	3c m.p. 131-2°C	(26%)	4c m.p. 126-7°C	(24%)
2-Thienyl	1d m.p. 124-5° C	3d m.p. 127-8°C	(28%)	4d m.p. 125°C	(25%)
Methyl	1e m.p. 91-2° C	3e m.p. 31-2°C	(25%)	4e m.p. 75-6°C	(24%)

TABLE I

The presence of the arylacyl functionality is not a prerequisite to the formation of these compounds since 3-acetamido-2-chloropyridine (1e) treated under similar conditions is converted into the expected 2-methylthiazolo and oxazolo[5,4-b]pyridines, (3e) and (4e) respectively.

However the structure of the parent arylamides strongly influences the reactivity. Thus treatment of compounds (5a,b) by the Lawesson Reagent (scheme II)



5a Ar = Ph

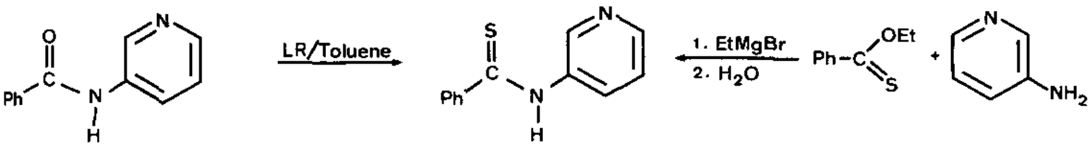
b Ar = p-Cl Ph

6a (66%)

b (64%)

Scheme II

yields the thiohomologues (6a,b) with good yields, whilst the reaction of the pyridinylarylamide (7a) with the same sulfurating agent and under similar conditions leads to the corresponding thioamide (8a) but with a very low yield (9%) (scheme III)[5]. However the thioamide (8a) is better prepared by condensation of ethyl thiobenzoate with the Grignard reagent of 3-aminopyridine[6] (yield 68%).

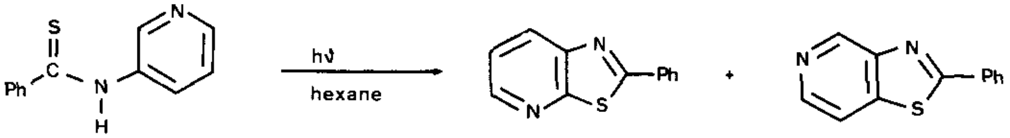


7a

8a

Scheme III

Pyridinylthioarylamides such as (8a) may also be regarded as precursors for various thiazolopyridines since photolysis of (8a)[7] in hexane gives rise to a mixture of 2-phenylthiazolo[5,4-b] and [4,5-c]pyridines (3a) and (9a) respectively[8] (scheme IV) :



Scheme IV

This photoreaction is rather similar to the photochemical conversion of thiobenzanilide into 2-phenylbenzo[b]thiazole[9].

REFERENCES AND NOTES

1. T.Y. Shen, R.L. Clark, A.A. Pessolano, B.E. Witzel, T.J. Jr. Lanza, Ger. Offen. 1974, 2 330 109 ; Chem. Abstr. 1974, **80**, 95916s.
2. The carboxamides (0.01 mole) and the Lawesson Reagent (LR) (0.005 mole) in 10 ml HMPA were heated at 140°C until the carboxamide had been consumed (TLC, about 2h).
3. S. Coffey, "Rodd's Chemistry of Carbon Compounds", Elsevier, Amsterdam, 1976, Vol. IV F, pp. 91-129.
4. All new compounds gave satisfactory elemental analysis and spectroscopic data.
5. Actually this seems to be a general phenomenon since thianation of various species such as ethyl 2-pyridinecarboxylate (S.L. Baxter, J.S. Bradshaw, J. Org. Chem. 1981, **46**, 831) and phenyl 2-pyridinyl ketone (B.S. Pedersen, S. Scheibye, N.H. Nilsson and S.O. Lawesson, Bull. Soc. Chim. Belges 1978, **87**, 223) has been reported to be difficult or impossible.
6. P. Reynaud, R.C. Moreau and J.P. Samana, Bull. Soc. Chim. France 1965, 3623.
7. Rayonet RPR 201 reactor, 300 nm and 350 nm lamps, 5×10^{-2} M solution, 12h.
8. Compounds (3a) and (9a) were separated on a silica gel column using toluene-ethylacetate 1:1 as eluant.
9. K.H. Grellmann, E. Tauer, Tetrahedron Lett. 1967, 1909.

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