SYNTHESIS OF NEW 1*H*-PYRAZOLO[3,4-*b*]PYRIDINE DERIVATIVES

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Abstract
A series of new 4-anilino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters (**2a-2h**) was synthesized as part of a program of study of potential antimalarial drugs. These compounds were obtained by a condensation reaction of 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine with several aniline derivatives. Some of them (**2c-2d**) were also obtained by an alternative pathway envolving a Mannich-type reaction with the 4-anilino derivatives (**2a-2b**).

Introduction

The antimalarial drugs, Chloroquine and Amodiaquine, are classified as "blood schizontocides". Resistance to choroquine in *Plasmodium falciparum* malaria has become a major health concern of the developing world. This resistance has prompted the study of new compounds that may be effective against resistant strains. Clinical experiences indicated that a radical cure could still be obtained with new compounds having similar structure of Amodiaquine. The strutures of which can be considered not only as 4-anilino-quinolines, but also as a Mannich base[1,2]. This early success estimulated many research groups to a search for other Mannich bases from the 1*H*-pyrazolo[3,4-*b*]pyridine system. Compounds having the 4-anilino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters system are related in the literature[3] as having good anxiolytic activity[4].

As part of an ongoing program toward the synthesis and study of new compounds with potencial antimalarial drugs, herein we are describing the synthesis of eight new 4-anilino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters (**2a-2h**). These compounds were obtained by a condensation reaction of 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine with several aniline derivatives. Some of them (**2c-2d**) were also obtained by an alternative pathway envolving a Mannich-type reaction with the 4-anilino derivatives (**2a-2b**).The complete synthetic sequence is outlined in **Scheme 1**.

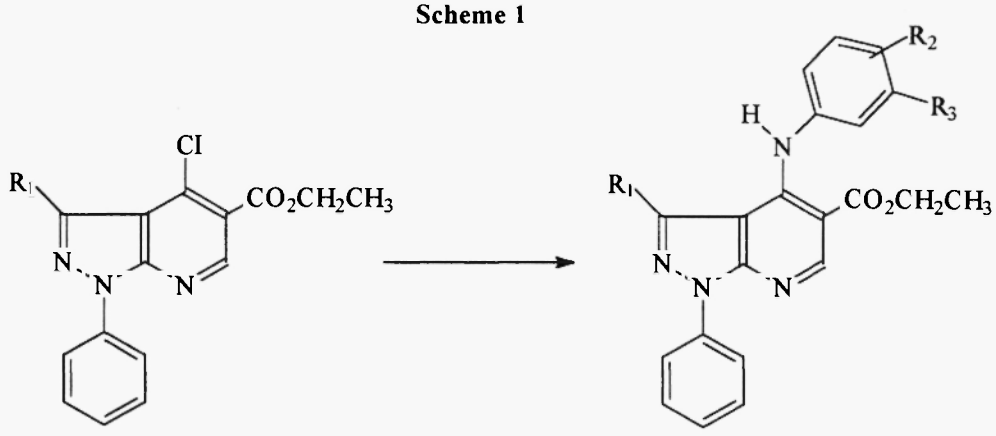
Results

The starting materials 4-chloropyrazolopyridines **1a** and **1b** were prepared as described in the literature.[5,6] Treatment of these compounds with p-aminophenol hydrochloride, in refluxing ethanol, for 48 hours, led respectively to **2a** (80% yield, mp 230-232°C) and **2b** (44% yield, mp 231-233°C). Substances **2c** and **2d** were obtained by two alternative pathways: reaction of **1a** and **1b** with diethylaminomethyl-4-acetylaminophenol[3], in refluxing benzene (dried before) for 24 hours (**2c**, 80% yield, mp 118-120°C; **2d**, 30% yield, mp 129-131°C); and the Mannich reaction performed with **2a** and **2b** and diethylamine/paraformaldehyde in isopropylic alcohol, under reflux[8] for 24 hours (**2c** and **2d** in 60% and 50% yields, respectively). Nucleophilic displacements of 4-halogen of **1b** by aniline, p-toluidine, p-nitroaniline and o-toluidine were carried out in refluxing toluene, yielding the desired compounds **2e** (2 h, 65%, mp 148-149°C), **2f** (2 h, 57%, mp 170-171 °C), **2g** (6 h, 50%, mp 230-233°C) and **2h** (6 h, 62%, mp 187-188°C).

All new compounds were purified by using vacuum liquid chromatography and were analysed by IR , ^{1}H and ^{13}C NMR spectroscopy[9], and high resolution mass spectrometry (**2a** calc. 388.1535, found 388.1540; **2b** calc.450.1698, found 450.1691; **2c** calc. 473.2427, found 473.2426; **2d** calc. 535.2582, found 535.2583; **2e** calc.

434.1747, found 434.1742; **2f** calc. 448.1897, found 448.1899; **2g** 479.1587, found 479.1593; **2h** calc. 4481895, found 448.1899).

Scheme 1



1a - R_1= CH_3
1b - R_1– Ph

2a- R_1= CH_3; R_2= p-OH; R_3= H
2b- R_1= Ph, R_2= p-OH; R_3= H
2c- R_1= CH_3; R_2= p-OH; R_3= $CH_2N(CH_2CH_3)_2$
2d- R_1= Ph; R_2= p-OH; R_3= $CH_2N(CH_2CH_3)_2$
2e- R_1= Ph; R_2= H; R_3= H
2f- R_1= Ph; R_2= p-CH_3; R_3= H
2g- R_1= Ph; R_2= p-NO_2; R_3= H
2h- R_1= Ph; R_2= o-CH_3; R_3= H

Conclusion

In conclusion, these eight new derivatives 4-anilino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters (**2a-2h**) were synthesized in good yields. The substances **2c** and **2d** were obtained by two different routes. The direct method[7] for producing the later compounds gave much better yields than the Mannich procedure[8].

Acknowledgments

The financial support from CNPq (PADCT 620587/91-1, Brazil, Nucleosides Synthesis), CNPq-PIBIC (Brazil) and CAPES (Brazil) is gratefully acknowledged. We also thank UFRJ and UFRRJ (Brazil) for NMR and MS spectra.

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Received June 28, 1996