NEW HETEROCYCLIC SYNTHESIS, CONVENIENT SYNTHESIS OF FUSED PYRIMIDINES, PYRAZOLES, AND TRIAZINES

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SUMMARY: A convenient synthesis of derivatives of the pyrimido (4', 5': 3,4) pyrazolo (3,2-c)-1,2,4-triazine and pyrazolo (3', 4': 3,4) pyrazolo (3,2-c) 1,2,4-triazine ring system from readily available 2-amino-3-cyano-6-methyl (phenyl)_pyrazolotriazine 1 and trichloroacetonitrile, phenylisothiocyanate, carbon disulphide and hydrazine is described.

Key Words: Pyrimidines, Pyrazoles, Triazines.

INTRODUCTION

Derivatives of the pyrazolopyrimidine ring system are known possess potent biological properties (1). As a part of our program (2) directed towards the synthesis of fused heterocyclic systems we become interested in new heterocyclic systems we became interested in new heteorcylic systems derived from pyrazolopyrimidine or pyrazolopyrasole. In this context, enamino-nitriles; which are versatile reagents and their chemistry has received considerable recent attention (3); served as the starting materials for the preparation of new heterocyclic tricyclic systems containing additionally a pyrimidine and/or pyrazolo fused ring. Reactivity of the readily available compounds 2-amino-3-cyano-6-methyl (phenyl)-pyrazolotriazine 1a, b towards activated nitriles was investigated, thus, it has been found that compound 1 reacts with the highly activated cyano group of trichloroacetonitrile in ethanol containing catalytic amount of triethylamine to give the pyrimido (4', 5': 3,4) pyrazolo (3,2-c)-1,2,4-triazine derivatives 2. The structure of 2 could be established for the reaction product based on ^{1}HNMR spectra which revealed a broad signals located at δ 6.48 ppm assignable to amino and hydroxy groups and a multiplet at δ 7.2-7.8 ppm assigned for aromatic protons. The formation of 2 might be assumed to proceed via addition of trichloroacetonitrile to yield the intermediate 3, which cyclizes under the reaction condition and then hydrolysed into the finally isolated product. The reaction of compound 1 with carbon disulphide in dimethylformamide in the presence of sodium ethoxide leads to the corresponding pyrimidopyrazolotriazines 4a, b. Structure 4 was established for this compound based on its ^{1}H NMR which revealed a NH singlet at δ 13.1 and 13.5 ppm and a multiplet at 7.2-8.1 ppm for aromatic protons. When compound 1 was treated with phenylisothiocyanate in benzene in the presence triethylamine pyrimidopyrazolotriazines 6 was obtained. The reaction possibly takes place through formation of the intermediate 5. On the other hand, compound 1 reacts with hydrazine in dimethylformamide at reflux temperature to give the pyrazolo (3',4': 3,4) pyrazolo (3,2-c)-1,2,4-triazines 7. The ^{1}H NMR spectrum of compound 7b shows signals at d 5.9,7.7, 8.25 ppm attributable to the NH groups and a multiplet at 7.35, 7.95 ppm for aromatic protons. This data was consistent with the structural assignments for compound 7.

These results indicate that the reaction of compound 1 with suitable active substituted nitriles, isocyanates and other reagents can be utilized as an effective route for the synthesis of several, otherwise difficulty accessible heterocyclic derivatives.

EXPERIMENTAL

Melting points are all uncorrected. IR spectra (KBr) were recorded on a Pye-Unicam SP-1100 spectrophotometer.^{1}H NMR spectra were recorded on a Varian EM

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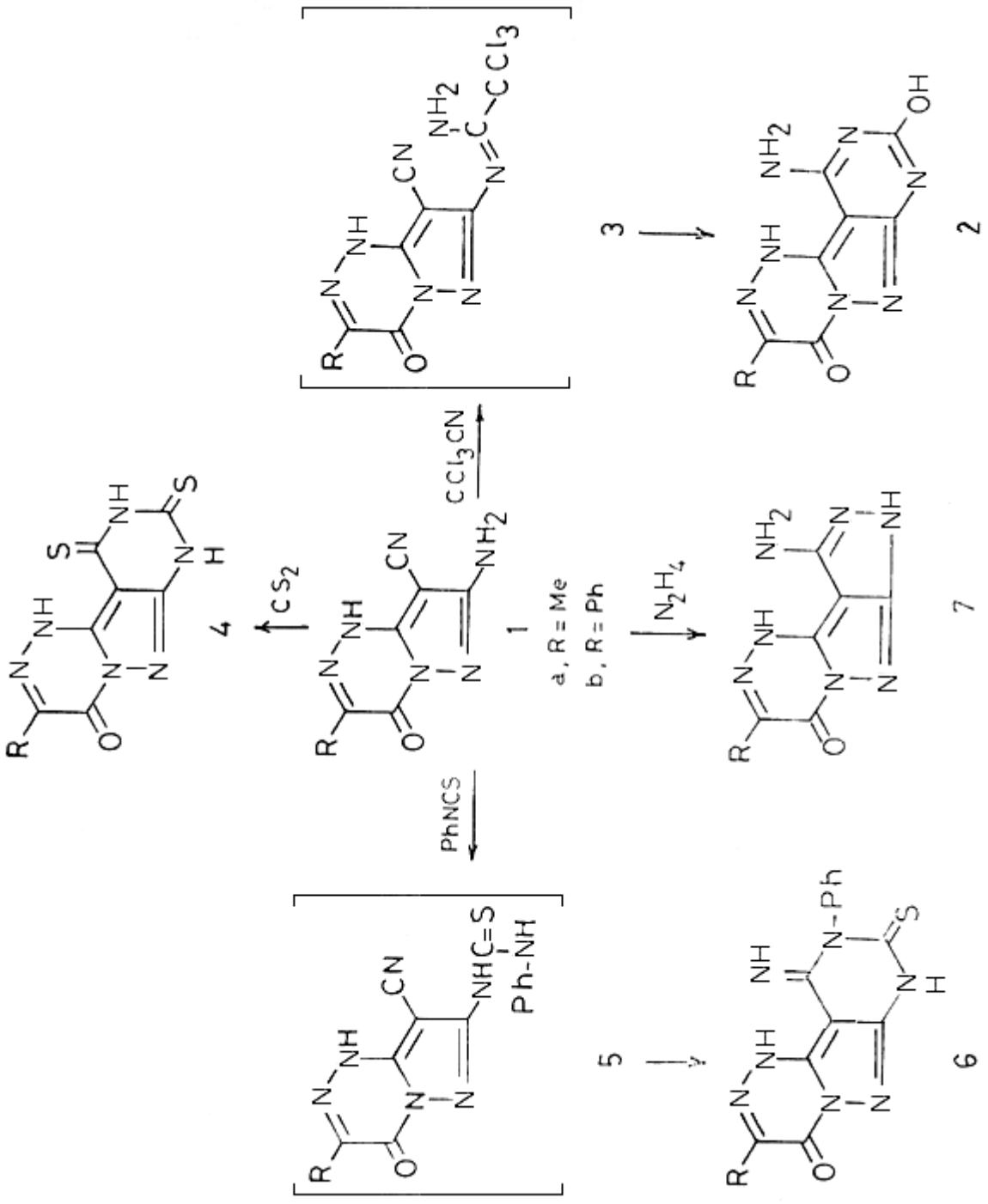

390 90 MHz using TMS as an internal standard. MS were recorded on a Finnigan MAT 312 (70eV). Microanalyses were carried out by the Microanalytical Centre, Cairo University. Compounds 1a, b were prepared following literature procedure (4).

Synthesis of compounds 2a, b:

General procedure:

A solution of each of compounds 1a, b (0.002 mole) and trichloroacetonitrile (0.0022 mole) in ethanol (35 ml) was heated under reflux for 6 h. After cooling the precipitate was collected and recrystallized from dimethylformamide to give 2a, b respectively.

Compound	Mp C	% Yield	Mol. Formula	Analysis		% Calcd. % Found	
				C	H	N	S
2a	>300	52	$C_8H_7N_7O_2$	41.56 41.50	3.05 2.80	41.54 41.90	
2b	>300	60	$C_{13}H_9N_2O_2$	53.24 53.50	3.09 3.00	32.75 32.30	
4a	>300	73	$C_8H_6N_6S_2O$	36.08 36.20	2.27 2.50	31.55 31.70	24.08 23.80
4b	>300	70	$C_{13}H_8N_6S_2O$	47.55 48.00	2.45 2.50	25.59 25.80	19.52 19.10
6a	>300	47	$C_{14}H_{11}N_7SO$	52.00 52.40	3.42 3.70	29.70 29.90	9.91 10.10
6b	>300	65	$C_{19}H_{13}N_7SO$	59.21 58.90	3.40 3.40	24.91 25.30	8.32 8.00
7a	285	48	$C_7H_7N_7O$	41.38 41.70	3.47 3.10	47.27 47.00	
7b	296	42	$C_{12}H_9N_7O$	54.34 53.90	3.42 3.10	36.21 36.50	

Synthesis of compounds 4a, b:

General procedure:

A solution of each of 1a, b (0.02 mole) and carbon disulphide (20 ml) in dimethylformamide (25 ml) containing sodium methoxide (prepared from 0.5 g of sodium and 15 ml of absolute methanol) was heated under reflux for 40 h. after cooling the precipitate was dissolved in 4 M sodium hydroxide solution, filtered and then the solution was acidified with dilute hydrochloric acid. The precipitate was collected, washed with water and then recrystallized from dimethylformamide to give 4a, b respectively.

Synthesis of compounds 6a, b:

General procedure:

A mixture of each of compounds 1a, b (0.02 mole) and phenylisothiocyanate (0.025 mole) in dry benzene (30 ml) and triethylamine (3 drops) was heated under reflux for 6 h. After cooling the precipitate was collected and recrystallized from dimethylformamide to give 6a, b respectively.

Synthesis of compounds 7a, b:

General procedure:

A mixture of each of 1a, b (0.5 g) and hydrazine hydrate (3 ml) in dimethylformamide (5 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was acidified with dilute hydrochloric acid till pH 6. The solid precipitate was collected, washed with water and recrystallized from dimethylformamide/ethanol mixture into 7a, b respectively.

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