Synthesis of Substituted Pyridine, Naphthyridine and Pyrido-Pyrimidine Derivatives

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Summary: Compound (1) reacted with malononitrile, phenyl isothiocyanate, urea and thiourea to give the pyridine derivatives (3), (4) and (6) respectively. Compound (2) reacts with the same reagents to give the naphthyridine derivative (8) and the pyrido-pyrimidine derivatives (9) and (10) respectively.

Introduction

The considerable biological activities of pyridine derivatives have stimulated enormous interest in the synthesis and chemistry of this class of compounds [1,2]. In previous work from our laboratory several pyridine derivatives have been obtained via reaction of cyanoacetanilide reacted with benzylidene malononitrile to yield the 2-pyridone derivative (1) [5]. On the other hand 2-pyridone derivative (2) was obtained upon reaction of cyanoacetanilide with anisylidene malononitrile [4]. In this paper compounds (1) and (2) were used as starting materials for the synthesis of substituted pyridine, naphthyridine and pyridopyrimidine derivatives.

The compound (1) reacts with malononitrile in ethanol and in the presence of catalytic amount of triethylamine to yield 4-amino-3-benzylidene-5-cyano-6-dicyano-methylene-pyridine-2-one (3) in excellent yield. Compound (3) was formed via simple condensation of active methylene in malononitrile with the carbonyl group in (1). This behaviour finds precedent in the reaction of 5-methylisatin with the same reagent [6].

The urea derivative (4) was obtained on reaction of (1) with phenyl isothiocyanate in pyridine. Compound (4) was formed via addition of the amino group from (1) to the reagent followed by hydrolysis of the sulphur under the reaction conditions to give the isolable product (4). Compound (1) also reacted with phenyl isocyanate to give (4) (m.p. and mixed m.p.).

Similarly compound (1) reacted with urea in alcoholic sodium ethoxide to give the urea derivative (6). The formation of (6) was suggested to proceed via attack of the nitrogen to C-4 in (1) to form the intermediate (5) and elimination of ammonia to give the final product (6). The structure of (6) was inferred from its correct analytical and spectral data. Compound (6) was also formed upon reaction of (1) with thiourea in sodium ethoxide (m.p. and mixed m.p.). The proposed thiourea derivative which has been formed as intermediate was hydrolyzed to the urea derivative (6) under the reaction conditions. Trials to affect cyclization of the products (4) and (6) via addition on the cyano function were failed.

In contrast to the behaviour of (1) towards malononitrile, phenyl isothiocyanate, urea and athiourea, compound (2) reacted with malononitrile to yield a product for which structure (8) was suggested based on analytical and spectral data. The formation of naphthyridine derivative (8) was assumed to proceed via the formation of the intermediate 1:1 adduct (7) followed by cyclization via loss of ethanol.

The pyrido-pyrimidinethione (9) was formed when (2) was reacted with phenyl isothiocyanate. Structure (9) was assigned for the reaction product based on elemental and spectral data. The formation of (9) was assumed to proceed via the same sequence as that illustrated for the formation of (8) and in addition the hydrolysis of the cyano group at C-3 was accomplished under the reaction conditions.

Compound (2) reacted with urea in sodium ethoxide to yield the pyrido-pyrimidine (10). Compound (10) was assumed to be formed via the same sequence illustrated for the reaction of (1) with urea to form the intermediate acyclic compound followed by cyclization via loss of water to afford the final product (10). Also compound (10) was obtained upon reaction of (2) with thiourea (m.p. and mixed m.p.). It can be postulated that the intermediate acyclic thiourea conditions which then cyclizes via loss of water to yield compound (10). The structure of (10) was inferred from its correct analytical and spectral data.

Experimental

All melting points are uncorrected. IR spectra were determined on a Pye Unicam SP 1000 instrument. Analytical data were obtained from the Microanalytical Data Unit at Cairo University.

The starting compounds (1) and (2) were prepared as described previously [4,5].

Reaction of (1) and (2) with manononitrile:

To a solution of (1) or (2) (0.01 mole) in ethanol (50 ml) malononitrile (0.01 mole) and triethylamine (1 ml) were added. The reaction mixture was refluxed for 6 h and evaporated in vacuo. The solid product formed was collected by filtration and crystallized from the proper solvent. The products were identified as (3) and (8) respectively (cf. the Table).

Reaction of (1) and (2) with phenyl isothiocynate:

A solution of (1) or (2) (0.01 mole) in pyridine (30 ml) was treated with phenyl isothiocyanate (0.01 mole) and the reaction mixture was refluxed for 5 h. The solvent was then removed by evaporation in vacuo. The oily residue was then triturated with alcohol, filtered off and crystallized from the proper solvent. The a products were identified as (4) and (9) respectively (cf. the Table).

Compound (1) also reacted with phenyl isocyanate under the above conditions to give (4) (m.p. and mixed m.p.).

Reaction of (1) and (2) with urea and athiourea:

To a solution of ethanolic sodium ethoxide prepared by dissolving 0.5 g of sodium metal in absolute ethanol (50 ml), was added compound (1) or (2) (0.01 mole) and urea or thiourea (0.01 mole). The reaction mixture was heated under reflux for 4 h then evaporated in vacuo. The resulting solid product, so formed, was collected by filtration and crystallized from the proper solvent. The products were identified as (6) and (10) respectively (cf. the Table).

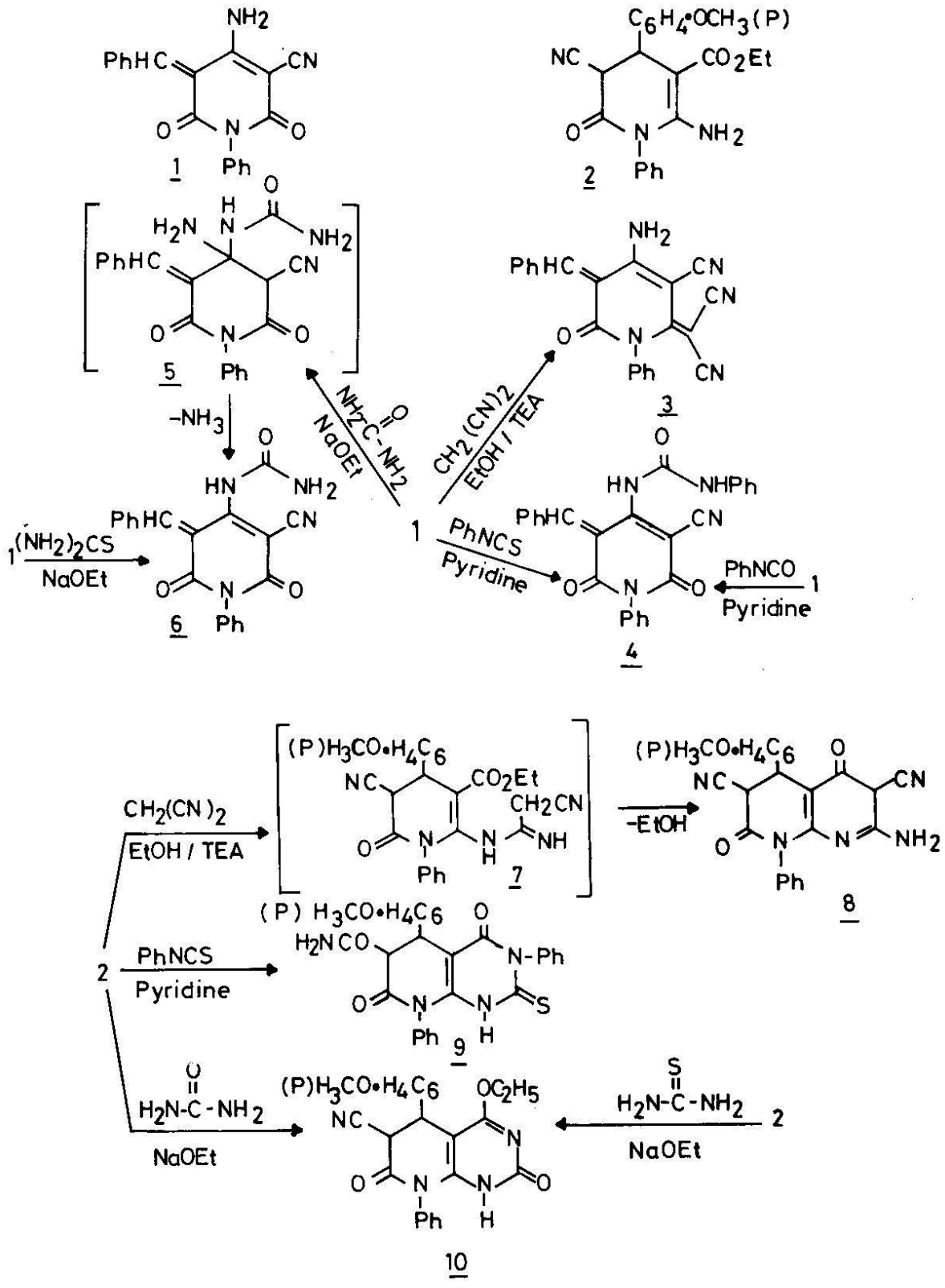
NH2
PhHC
CN
O
N
O
Ph
1
C6H4•OCH3(P)
NC
CO2Et
NH2
2
H2N
NH2
5
-NH3
NH2-C-NH2
NaOEt
CH2(CN)2
EtOH / TEA
3
CN
6
(NH2)2CS
NaOEt
PhNCS
Pyridine
NHPh
4
PhNCO
Pyridine
CH2(CN)2
EtOH / TEA
(P)H3CO•H4C6
CO2Et
CH2CN
NH
7
-EtOH
8
PhNCS
Pyridine
H2NCO
N-Ph
S
9
H2N-C-NH2
NaOEt
OC2H5
10

Table-1: Characterization data of the newly synthesized compounds.

Compound* (Colour)	Crystallization Solvent	M.P. °C	Yield %	Molec.Formula (Mol.Wt.)	Analysis (%) Calcd/Found C	H
(3) (pale yellow)	Dioxan	278	77	$C_{22}H_{13}N_5O$ (363)	72.7 (72.5)	3.6 (3.9)
(4) (yellow)	Alcohol	270	65	$C_{26}H_{18}N_4O_3$ (434)	71.9 (72.1)	4.1 (4.0)
(6) (pale yellow)	Dioxan	305	63	$C_{20}H_{14}N_4O_3$ (358)	67.0 (67.3)	3.9 (4.0)
(8) (colourless)	Alcohol	285	58	$C_{23}H_{17}N_5O_3$ (411)	67.2 (66.8)	4.1 (4.0)
(9[x]) (colourless)	Alcohol	286	72	$C_{27}H_{22}N_4O_4S$ (498)	65.1 (65.0)	4.4 (4.4)
(10) (colourless)	Alcohol	245	63	$C_{23}H_{20}N_4O_4$ (416)	66.3 (66.5)	4.8 (5.0)

* Satisfactory IR spectra for all compounds were obtained.

x Analysis for S, Calcd.: 6.4, Found: 6.2.

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