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A Facile Synthesis of Pyrimidoquinazoline Derivatives

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ABSTRACT

A series of pyrimidoquinazoline are prepared via the reaction of ethyl 2,2-dicyano-1-arylvinylcarbamate derivatives **1a-b** with methyl 2-aminobenzoate, 1-(2-aminophenyl)ethanone and 2-aminobenzonitrile. The reactivity of compounds **1a-b** toward 3-amino-4,6-diphénylnicotinonitrile are studied. The structures of the synthesized compounds are elucidated by X-ray diffraction, IR spectroscopy and nuclear magnetic resonance.

Keywords

Pyrimidoquinazoline; pyrimidine; X-ray diffraction; Infrared spectroscopy; Nuclear magnetic resonance.

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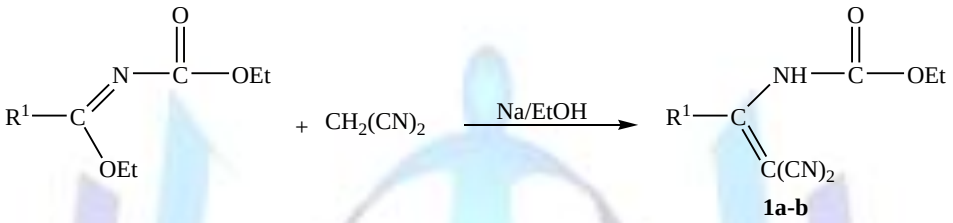
INTRODUCTION

Pyrimidoquinazoline compounds have fascinated researchers for a long time; they are used in a wide range of applications in pharmaceutical chemistry. Multiple methods of preparation of these compounds have been developed [1-5], they've come up with the result that pyrimidoquinazoline derivatives exhibit anti-inflammatory [6, 7], anti-cancer [7] and antioxidant activities [8].

In search of an efficient method of preparation of pyrimidoquinazoline compounds, and following our work on synthesis of polyheterocyclic systems which contain pyrimidinone moiety [9-11], we report here the synthesis of some new pyrimido[1,6-a]quinazoline-4-carbonitrile and tetrahydropyrimidine-5-carbonitrile derivatives.

RESULTS AND DISCUSSION

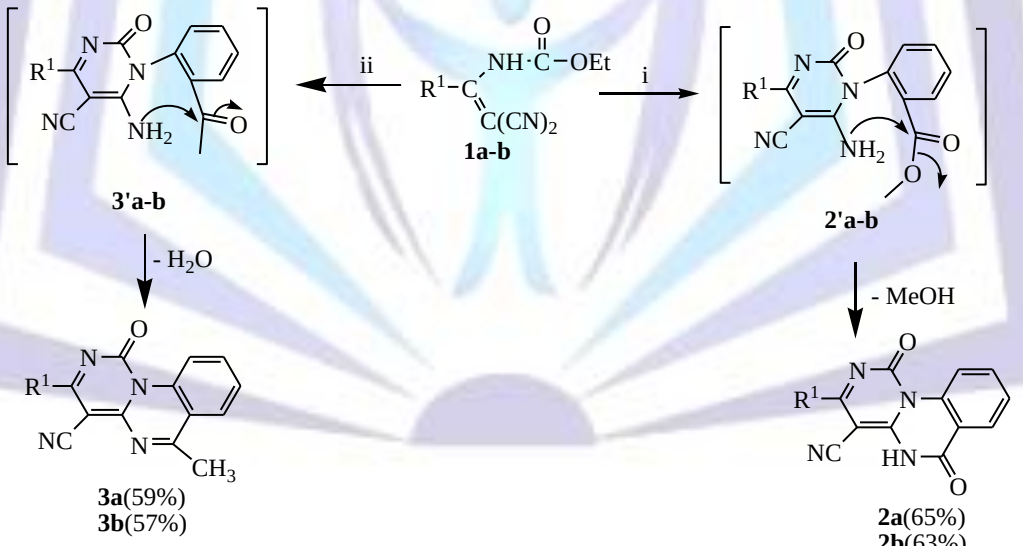
The ethyl 2,2-dicyano-1- arylvinylcarbamate derivatives **1a-b**, used in this study, are prepared by condensation of malononitrile with ethyl N-(ethoxycaronyl)imidates by a previously reported method [12].



1a:R^1= C_6H_5; **1b**:R^1= pMeC_6H_4

Scheme 1: Synthetic route to ethyl 2,2-dicyano-1-arylvinylcarbamate

Condensation of substrates **1a-b** (which contain functionality (CN and CO)) with methyl 2-aminobenzoate or 1-(2-aminophenyl) ethanone in chlorobenzene for 4h give tricyclic 1*H*-pyrimido[1,6-a]quinazoline-4-carbonitrile derivatives **2a-b** and **3a-b**. The first step of the mechanism involves the condensation of the NH_2 group with ester and cyano groups of **1a-b**, in which the nonisolable intermediates **2'a-b** and **3'a-b** are obtained first, then, followed by an internal nucleophilic attack by the NH_2 group of the pyrimidinone ring on the ester or ketone group to yield **2a-b** and **3a-b** (Scheme 2).



i : methyl 2-aminobenzoate; ii : 1-(2-aminophenyl)ethanone

Scheme 2: Synthetic route to pyrimidoquinazoline

In the ^{1}HNMR spectra (**2a-b**) the most significant information is the disappearance of the methoxy group's singlet of the starting reagent methyl 2-aminobenzoate. This proves that the amino group attacks the ester function. In the IR spectra (**3a-b**), the absorption band at around 3200-3400 cm^{-1} corresponding to amino group, is not observed. The ^{1}HNMR spectra shows the presence of methyl group from the cycloadduct **3a** at δ 3.02 (s, 3H, CH_3-C=N-) and tow methyl groups from the cycloadduct **3b** at δ 2.42(s, 3H, CH_3-C_6H_4-) and δ 3.02 (s, 3H, CH_3-C=N-).

Moreover, heating compounds **1a-b** and 2-aminobenzonitrile in chlorobenzene leads to the formation of the corresponding pyrimidinone **4'a-b** or pyrimidoquinazoline derivatives **4a-b** (Scheme 2). Regarding the last reaction (formation of **2a-b** and **3a-b**) we can hypothesize the formation of compounds **4a-b**. Yet, spectral data does not show exactly which product is formed **4a-b** or **4'a-b**.

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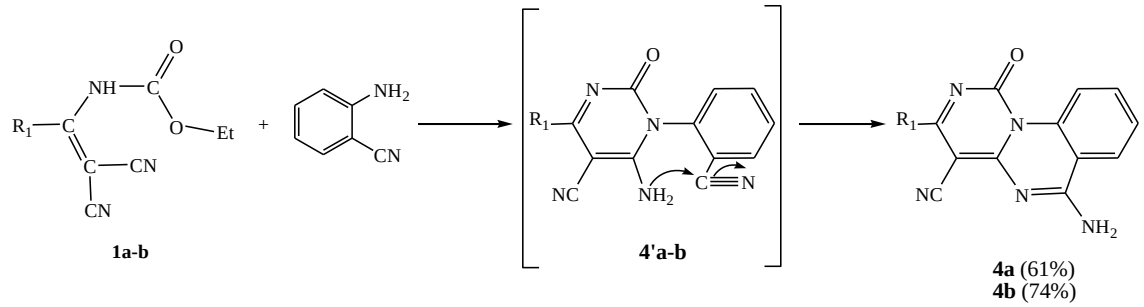


Scheme 3: Synthetic route to 6-amino-pyrimidoquinazoline

In order to know which specific product is formed, an X-ray crystallographic study of the compound **4a** was carried out (Figure 1). This study, showed only the formation of compounds **4a-b** and not **4'a-b**.

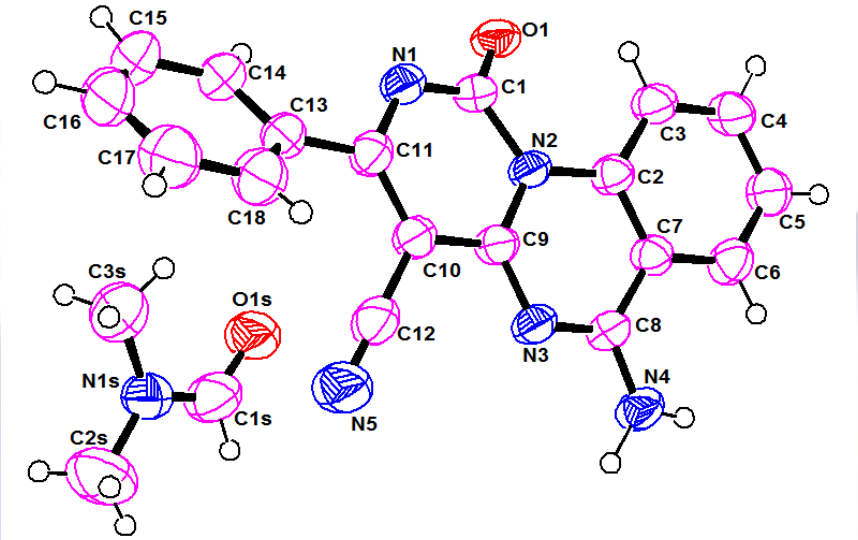
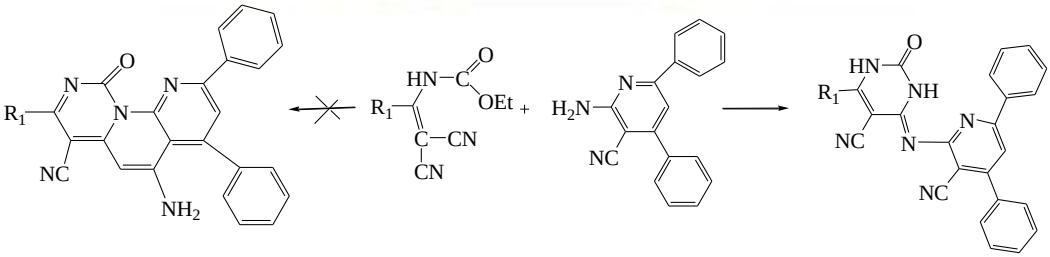


Figure 1: X-ray crystal analysis of the compound **4a**

X-ray data diffraction of the compound **4a**: $C_{21}H_{18}N_6O_2$, M = 386.41 g.mol^{-1}, monoclinic, space group $P2_1/c$, a = 16.077 (9), b = 16.228 (9), c = 7.484 (4) Å, β = 91.296 (10) °, V = 1951.8(19) Å^3, Z = 4, 1563 reflections with I>2σ(I) used for the refinement of the crystal structure. The final discrepancy factors R_1 and wR_2 were found to be 0.058 and 0.137.

Furthermore, the reaction of **1a-b** with 3-amino-4,6-diphénylnicotinonitrile afforded 1,2,3,4-tetrahydropyrimidine - 5-carbonitrile derivatives **5a-b** and not pyrimidoquinazoline **5'a-b** structures (Scheme 4).



Scheme 4

The structures of compounds **5a-b** are congruent with their spectral data. The decoupled ^{13}CNMR spectra show two signals at δ 115-118. This is due to the carbon atom in the two cyano groups. Besides, ^{1}HNMR spectra indicate two

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singlets at δ 12.20-13.20 for the two NH groups. To confirm the suggested structures, the compound **5a** was analyzed by X-ray diffraction.

X-ray results indicate the formation of the compound **5a** and not **5'a** (Figure 2).

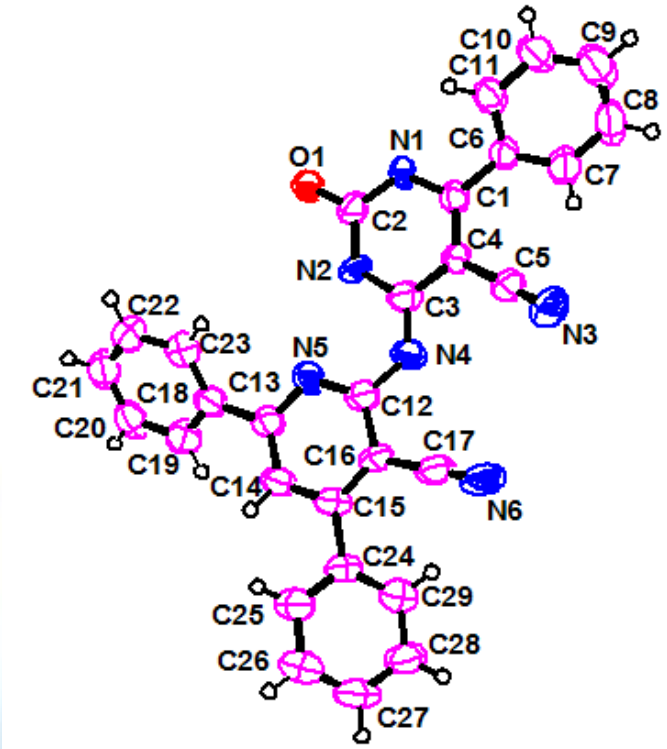
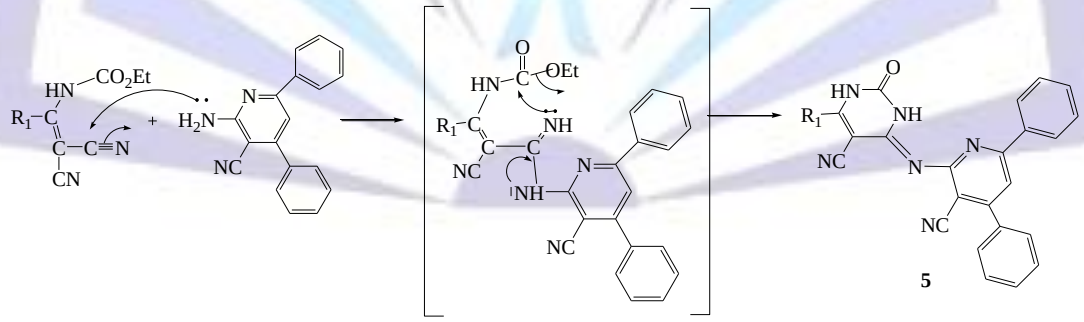


Figure 2: X-ray crystal analysis of the compound **5a**

X-ray data diffraction of the compound **5a**: $C_{29}H_{18}N_6O$, M = 466.49 g.mol^{-1}, monoclinic, space group $P2_1/n$, a = 10.635 (2), b = 25.782 (5), c = 17.906 (3) Å, β = 107.028 (3) °, V = 4694.8 (2) Å^3, Z = 8, 2782 reflections with I>2σ(I) used for the refinement of the crystal structure. The final discrepancy factors R_1 and wR_2 were found to be 0.073 and 0.167.

We suggest the following mechanism: first, the formation of nonisolable intermediate by condensation of the NH_2 group with cyano group of **1a-b** followed by an internal nucleophilic attack by the NH leading to our product (Scheme 5).



Scheme 5

CONCLUSION

In conclusion, in this work we have reported the synthesis of some new pyrimidoquinazoline and pyrimidine derivatives. Results demonstrate that 2-aminobenzonitrile and 3-amino-4,6-diphénylnicotinonitrile react differently to the compound **1a-b** even though they have the same functions.

ISSN 2321-807X

EXPERIMENTAL

Melting points are recorded in degrees Celsius on a Kofler apparatus. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), with UV detection at 254 nm. The IR spectra were recorded in the solid state as KBr discs on a Perkin-Elmer PARAGON 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR were determined in solution in DMSO-d_6 with an AC Bruker spectrometer at 300 MHz using TMS as an internal standard. The mass spectra were recorded on an ion trap mass spectrometer (Finnigan LCQ Deca XP Max) using electrospray as an ionization source. The purity of all compounds was determined by LC-PDA-MS methods and was found to be in the range between 96-99%.

A suitable crystal was carefully selected under a polarizing microscope and mounted at the end of a thin glass fiber. Crystal structures determination were performed using a BRUKER SMART APEX CCD diffractometer which uses graphite monochromatized MoKα radiation (λ = 0.71073 Å). Unit cell parameters, optimized by least-squares refinement were calculated and refined using indexation of collected intensities. Structures were solved by direct methods using SHELXS-97 [13] and refined by full-matrix least-squares procedures using the SHELXL-97 program [14].

GENERAL EXPERIMENTAL PROCEDURE

To a magnetically stirred solution of the ethyl 2,2-dicyanolvinylcarbamate derivatives **1a-b** (0.255 g: 1 mmol) in chlorobenzene (10 mL), the appropriate amines (1.2 mmol) were added and the reaction mixture stirred for 2~4 h at 110 °C. The progress of the reaction was monitored by TLC (mobile phase, ethyl acetate: dichloromethane; 60/40;v/v). The resulting mixture was allowed to cool at room temperature. The precipitate formed was isolated by filtration and washed with diethyl ether to obtain the pure product.

Spectral Data of New Compounds

1,6-dioxo-3-phenyl-5,6-dihydro-1H-pyrimido[1,6-a]quinazoline-4-carbonitrile (**2a**). Rdt (63%), $C_{18}H_{10}N_4O_2$, M=314g.mol^{-1}, mp> 300°C; IR (KBr) v:3204 (NH), 2236 (CN), 1756 (C=O), 1688 (C=O), 1624 (C=N) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 7.49–8.20 (m,10H, Ar-H + NH); ^{13}C-NMR (DMSO-d6): δ = 59.1 (C4), 115.5 (**C**N), 148.0 (C=**C**-N), 157.1 (C1), 159.0 (C6), 169.5 (C3), 120.9-147.8(C_{arom}); MS-(+)ESI: *m/z* (%):315 ([M+H]$^+$, 100).

1,6-dioxo -3-p-tolyl-5,6-dihydro-1H-pyrimido[1,6-a]quinazoline-4-carbonitrile (**2b**). Rdt (65%), $C_{19}H_{12}N_4O_2$, M=328g.mol^{-1}, mp= 275°C; IR (KBr) v:3225 (NH), 2218 (CN), 1748 (C=O), 1685 (C=O), 1619 (C=N) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 2.1(s, 3H, CH_3), 7.36–8.08 (m,9H, Ar-H + NH); ^{13}C-NMR (DMSO-d6): δ = 20.8 (**C**H$_3$), 87.1 (C4), 116.6 (**C**N), 149.8 (C=**C**-N), 157.8 (C1), 158.8 (C6), 167.5 (C3), 120.3-147.4(C_{arom}); MS-(+)ESI: *m/z* (%):329([M+H]$^+$,100).

6-methyl-1-oxo-3-phenyl-1H-pyrimido[1,6-a]quinazoline-4-carbonitrile (**3a**). Rdt (57%), $C_{19}H_{12}N_4O$, M=312g.mol^{-1}, mp= 256°C; IR (KBr) v: 2224 (CN), 1720 (C=O), 1595 (C=N) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 3.02 (s, 3H), 7.26–8.39 (m,9H, Ar-H); ^{13}C-NMR (DMSO-d6): δ = 23.9 (**C**H$_3$), 84.3 (C4), 116.6 (**C**N), 156.7 (C=**C**-N), 169.6 (C1), 175.0 (C3), 120.1-136.3(C_{arom}); MS-(+)ESI: *m/z* (%):313 ([M+H]$^+$, 100).

6-methyl-1-oxo-3-p-tolyl-1H-pyrimido[1,6-a]quinazoline-4-carbonitrile (**3b**). Rdt (59%), $C_{20}H_{14}N_4O$, M=326g.mol^{-1}, mp= 257°C; IR (KBr) v: 2222 (CN), 1705 (C=O), 1595 (C=N) cm^{-1}; ^{1}H-NMR: (DMSO-d6): δ = 2.42 (s, 3H), 3.02 (s, 3H, CH_3), 7.32–8.42 (m,8H, Ar-H); ^{13}C-NMR (DMSO-d6): δ = 21.5 (**C**H$_3$), 23.8 (**C**H$_3$), 86.2 (C4), 116.7 (**C**N), 156.8 (C=**C**-N), 169.5 (C1), 174.8 (C3), 120.4-142.6(C_{arom}); MS-(+)ESI: *m/z* (%):327 ([M+H]$^+$, 100).

6-amino-1-oxo-3-phenyl-1H-pyrimido[1,6-a]quinazoline-4-carbonitrile **(4a)**. Rdt (61%), $C_{18}H_{11}N_5O$, M=313g.mol^{-1}, mp> 300°C; IR (KBr) v: 3420–3332 (NH2), 2209 (CN), 1713 (C=O) cm^{-1}; ^{1}HNMR(DMSOd$_6$):δ=7.5-9.2(m,9H,H_{arom}); 9.3(s,2H,NH_2). ^{13}CNMR(DMSO-d$_6$): 81.6 (C4); 117.3(**C**N); C_{arom},120.8-136.4 ; 152.6 (C1); 157.7 (C6) ; 160.1(C3); 169.3 (C5); MS-(+)ESI: *m/z* (%):314 ([M+H]$^+$, 100).

6-amino-1-oxo-3-p-tolyl-1H-pyrimido[1,6-a]quinazoline-4-carbonitrile **(4b)**. Rdt (74%), $C_{19}H_{13}N_5O$, M=327g.mol^{-1}, mp> 300°C; IR (KBr) v: 3440–3312 (NH2), 2211 (CN), 1679 (C=O) cm^{-1}; ^{1}HNMR(DMSOd$_6$):δ= 2.41 (s, 3H, CH_3), 7.3–9.2 (m,8H, H_{arom}), 9.3 (s, 2H, NH_2).^{13}CNMR(DMSO-d$_6$): 21.5(**C**H$_3$), 81.8 (C4); 118.0 (CN); C_{arom},121.3-141.9 ; 153.1 (C1); 158.2(C6); 160.5 (C3); 169.5 (C5); MS-(+)ESI: *m/z* (%):328 ([M+H]$^+$, 100).

(Z)4-(3-cyano-4,6-diphenylpyridin-2-ylimino)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **(5a):** Rdt (58%), $C_{29}H_{18}N_6O$, M=466g.mol^{-1}, mp> 300°C ; IR (KBr) v: 3421 (NH), 2228 (CN), 1702 (C=O); ^{1}HNMR (DMSOd$_6$):δ= 7.4-7.80(m,16H,H_{arom}); 12.28(s,1H,NH); 13.20(s,1H,NH); ^{13}CNMR(DMSO-d$_6$): 87.5(C5); 115.35 and 116.48 (CN); C_{arom},128.05-137.75; 148.51(C2); 152.39(C6); 161.55(C4) ; MS-(+)ESI: *m/z* (%):467 ([M+H]$^+$, 100).

(Z)-4-(3-cyano-4,6-diphenylpyridin-2-ylimino)-2-oxo-6-p-tolyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **(5b):** Rdt = (53%); $C_{30}H_{20}N_6O$, M=480g.mol^{-1}, mp> 300°C; IR (KBr) :v =3467(NH), 2229 (CN), 1693 (C=O); ^{1}HNMR (DMSOd$_6$):δ=2. 5(s, 3H) , 7.5-8.25(mu ,15H_{arom}), 12.34(s,1H,NH); 13.15(s,1H,NH); ^{13}CNMR(DMSO-d$_6$): 20.0 (**C**H$_3$); 87.83 (C5); 116.11 and 117.93 (CN), 128.41-137.68 (C_{arom}); 149.32(C2); 152.15(C6); 158.35(C4); MS-(+)ESI: *m/z* (%):481 ([M+H]$^+$, 100).

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