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Synthesis and Ring Transformation of Pyrrolo[2,3-d][1,3]oxazine to Pyrrolo[2,3-d]pyrimidines

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Abstract□A convenient route is reported for the synthesis of fused pyrrolo [2, 3-d] [1, 3]-oxazine and pyrrolo [2, 3-d]-pyrimidine derivatives from 2-amino-1-benzyl-3-t-butoxy-carbonyl-4, 5-dimethylpyrrole.

Keywords□Transformation, pyrrolo [2,3-d]-pyrimidine.

Pyrrolo[2,3-d]pyrimidines have been of major medicinal interest in recent years following the discovery of their nucleus in some compounds with antibiotic[1-4], and antitumor activities[5]. This led the author to prepare 7-benzyl-2,5,6-trimethylpyrrolo [2,3-d][1,3]oxyzin-4-one and investigate its reactivity towards transformation to several new fused pyrrole-heterocyclic ring system, specifically pyrrolo [2,3-d] pyrimidines for their medicinal interest.

RESULTS AND DISCUSSION

In the initial step for synthesis of 7-benzyl-2, 5,6-trimethylpyrrolo[2,3-d] [1,3] oxazin-4-one (IV), 2-amino-3-t-butoxycarbonyl-4, 5-dimethylpyrrole (III) was prepared by a modified Bayomi procedure[6, 7]. In this synthesis, tert-butylcyanoacetate was refluxed with aminoketone (II), obtained from the condensation of acetyl carbinol (I) with benzylamine Scheme 1.

Refluxing of 2-amino-1-benzyl-3-t-butoxycarbonyl-4,5-dimethylpyrrole (III) with acetic acid/ acetic anhydride mixture containing sodium acetate for 2 hours gave 7-benzyl-2,5,6-trimethylpyrrole [2,3-d][1,3]oxazine-4-one (IV) in good yield.

The infrared and ^{1}H-NMR spectra of IV were consistent with the assigned structure. The compound showed typical carbonyl absorption in the region 1775 and 1690 cm^{-1}. In ^{1}H-NMR spectrum, the methyl groups appeared as a sharp singlets at 1.93 and 2.10 for pyrrole methyl groups and at 2.25 for the oxazine methyl group.

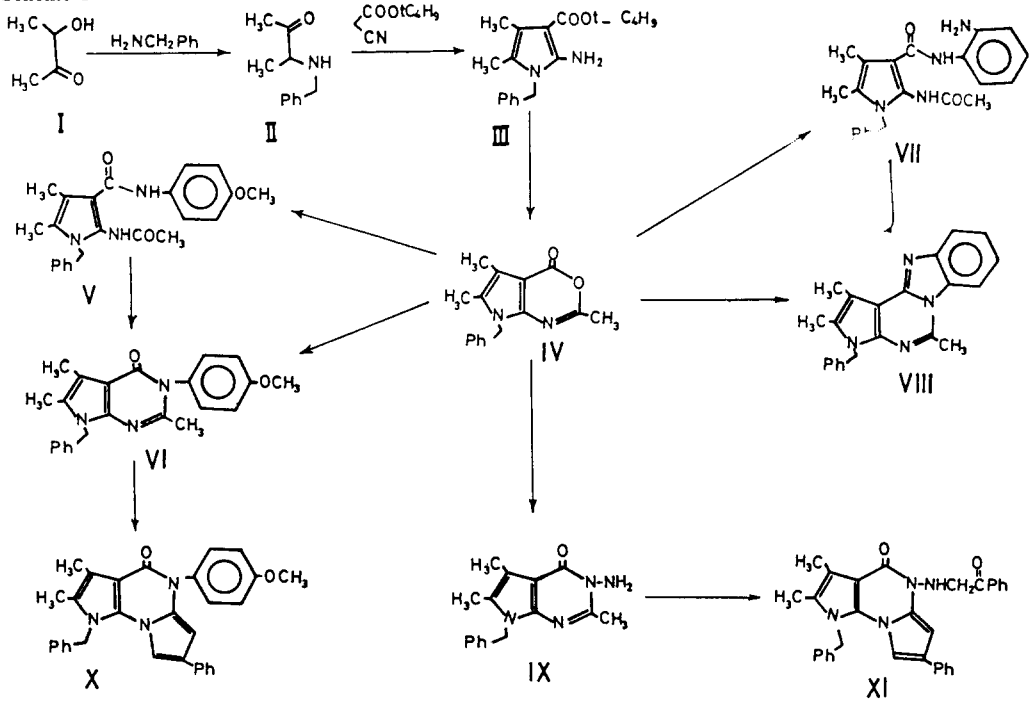
The benzyl-2,5,6-trimethylpyrrolo[2,3-d][1,2]oxazine-4-one (IV) underwent ring transformation reactions when treated with aromatic amines under different reaction conditions. Thus, when IV reacted with p-methoxyaniline in ethyl alcohol gave 1-benzyl-2-acetamido-3-[(p-methoxyphenyl) carboxamido]-4,5-dimethylpyrrole (V) in high yield. while, when the reaction carried out in acetic acid containing sodium acetate, IV under-went ring conversion to give 7-benzyl-2,5,6-trimethyl-3-(p-methoxyphenyl)pyrrolo[2,3-d]pyrimidin-4-one (VI). Compound VI could be also obtained upon refluxing the open product V in acetic acid containing sodium acetate.

Consequently, refluxing pyrrolo [2,3-d][1,3]oxazine-4-one (IV) with o-phenylenediamine in ethanol, afforded 1-benzyl-2-acetamido-3-(2-aminocarbamoyl)-4,5-dimethylpyrrole (VII), which cyclizes to 1-benzyl-2,3,10-trimethylpyrrolo[2,3-d]pyrimidino[1,6-a]benzimidazole(VIII), upon refluxing in acetic acid containing sodium acetate. Compound VIII was also obtained directly by reacting pyrrolo[2,3-d][1,3]oxazin-4-one (IV) with o-phenylenediamine in acetic acid containing sodium acetate.

On the other hand, reaction of pyrrolo[2,3-d][1,3]oxazin-4-one (IV) with hydrazine hydrate in acetic acid containing sodium acetate afforded 3-amino-7-benzyl-2,5,6-trimethylpyrrolo[2,3-d]pyrimidin-4-3H-one (IX) in good yield.

Interestingly, reaction of Compound VI and IX with phenacyl bromide in ethanol containing potassium carbonate, afforded the unexpected 1-benzyl-2, 3-dimethyl-5-(p-methoxyphenyl)-7-phenylpyrrolo[2,3-d]pyrimidino[1, 2-a] pyrrole (X) and

Scheme 1



1-benzyl-2, 3-dimethyl-5-N-(benzoylmethylamino)-7-phenylpyrrolo[2,3-d]pyrimidino[1,2-a]pyrrole (XI) respectively,[8, 9] Scheme 1.

The structures were assigned on the basis of characteristic ^{1}H-NMR spectra where the 6-methyl signal at 2.25 for compound VI and IX was disappeared in the new product spectra and the appearance of new singlet at 6.20 for the pyrrole equivalent olefinic protons at C_6 and C_8 positions. In addition the multiplicity of the aromatic proton signals due to the newly added phenyl group.

All the synthesized compound gave satisfactory spectral data and the structures were assigned on the basis of elemental analysis Table I, IR (potassium bromide) and ^{1}H-NMR spectral data given in the experimental section.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Nuclear magnetic resonance spectra were determined on a Varian FT80A or EM360A Spectrometer using tetrametylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer 580-B spectrophotometer using the potassium bromide technique. Elemental analysis were done with Perkin-Elmer 240B analyser.

2-Amino-1-benzyl-3-tert-butoxycarbonyl-4, 5-dimethylpyrrole (III)

A mixture of acetoin (acetyl ethyl carbinol 85% aqueous solution)[1] (5.25g, 0.05 mole) and benzylamine (5.35g, 0.05 mole) in cyclohexane (30 m*l*) was refluxed with a Dean-Stark trap until the separation of water (1.4 m*l*) has ceased (≃30 min.). After cooling the mixture to room temperature, tert. butyl cyanoacetate (7.5g, 0.055 mole) was added and the solution was refluxed for 2 hours, with collection of additional 0.8 m*l* of water. The cyclohexane was removed *in vacuo* and the residue was crystallized from 40 m*l* methanol/water (3:1) after standing overnight in the freezer. The crude product (13g, 88%) was further recrystallized from 50 m*l* of methanol/water (7:3) to yield off-white crystals m.p. 93-94°[6], IR (KBr) 3420 (NH_2), 1660 (C=O) cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ : 1.52 (s, 9H, methyls of tert. butoxycarbonyl), 2.0 (s, 3H methyl at C_4), 2.1 (s, 3H, methyl at C_5), 4.65 (broad s, 2H, amino group), 4.75 (s, 2H, benzylic methylene), 6.85-7.25 (m, 5H, aromatic protons). For the physical constants see Table I.

1-Benzyl-2,5,6-trimethylpyrrolo[2,3-d][1,3] oxazine-4-one (IV)

A solution of 2-amino-1-benzyl-4,5-dimethylpyrrole (III) (3.0g, 0.01 mole) in a mixture of ace-

Table I. Physical and analytical data of the synthesized compounds

Compound No.	Yield %	M.p°C	Molecular formula	Analysis % Caled (Found)		
				C	H	N
IV	65	139-40	$C_{16}H_{16}N_2O_2$	71.64 (71.56)	5.97 (5.91)	10.45 (10.42)
V	55	125- 6	$C_{23}H_{25}N_3O_3$	70.59 (70.65)	6.39 (6.33)	10.62 (10.45)
VI	75	91- 2	$C_{23}H_{23}N_3O_3$	73.97 (73.99)	6.20 (6.17)	11.25 (10.90)
VII	71	85- 7	$C_{22}H_{24}N_4O_2$	70.18 (70.45)	6.42 (6.81)	14.88 (14.35)
VIII	52	195- 7	$C_{22}H_{20}N_4$	77.61 (76.97)	5.92 (6.31)	16.45 (16.13)
IX	55	210- 7	$C_{16}H_{18}N_4O$	68.06 (68.31)	6.42 (6.12)	19.84 (19.62)
X	56	70- 2	$C_{31}H_{27}N_3O_2$	78.62 (78.59)	5.74 (5.55)	8.87 (8.67)
XI	58	242- 3	$C_{32}H_{28}N_4O_2$	76.77 (76.29)	5.63 (5.45)	11.19 (12.30)

tic anhydride (24 m*l*) and acetic acid (15 m*l*) containing sodium acetate (2.0g) was refluxed for two hours. The precipitate formed after cooling was collected and recrystallized from ethanol to give colourless crystals of IV; IR (KBr) 1640 (C = N) and 1780 (C-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.93 (s, 3H, CH_3 at C_4), 2.10 (s, 3H, -CH_3 at C_5), 2.25 (s, 3H, CH_3 at 6-position), 5.20 (s, 2H, benzylic methylene), 6.9-7.4 (m, 5H, aromatic protons).

1-Benzyl-2-acetamido-3-[(p-methoxyphenyl) carboxamido]-4, 5-dimethylpyrrole (V)

A mixture of IV (2.68g, 0.01 mole) and p-anisidine (1.23g, 0.01 mole) was refluxed in ethanol (50 m*l*) for two hours and cooled to room temperature. The crude product was collected by filtration and recrystallized from ethanol to give buff crystals of V (2.2g); IR (KBr) 1640 (C = N) and 1710 (CONR) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 2.0 (s, 3H, CH_3 at C_5), 2.45 (s, 3H, $COCH_3$) 6.85-7.35 (m, 9H aromatic protons), 10.2 (broad s, NH).

7-Benzyl-2,5,6-trimethyl-3-(p-methoxyphenyl) pyrrolo [2, 3-d]pyrimidin-4 (2H)-one (VI)

A mixture of pyrrolo [2, 3-d] [1, 3] oxazin-4-one (IV) (2.68g, 0.01 mole) and p-anisidine (1.23g, 0.01 mole) in glacial acetic acid (20 m*l*) containing fused sodium acetate (1g) was refluxed for one hour. After cooling, the precipitate was collected by filtration and recrystallized from ethanol to give a brown crystals of VI (2.8g); IR (KBr) 1640 (C = N) and 1705 (CONR) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 2.0 (s, 3H, CH_3 at C_4), 2.15 (s, 3H, CH_3 at C_5), 2.25 (s, 3H, CH_3 at C_6), 3.85 (s, 3H, OCH_3), 5.25 (s, 2H, benzylic protons), 6.5-7.75 (m, 9H, aromatic protons).

Cyclization of 1-benzyl-2-acetamido-3-(p-methoxyphenyl)caroxamido-4,5-dimethylpyrrole (V) to VI

A mixture of compound V (3.0g, 0.01 mole) in glacial acetic acid (20 m*l*) containing sodium acetate (1g) was refluxed for 2 hours. The precipitated solid after coding was collected and recrystallized from ethanol to afford brown crystals with the same melting point and ^{1}H-NMR spectrum of Compound VI obtained above.

1-Benzyl-2-acetamido-3-(2-aminophenyl)carboxamido-4, 5-dimethylpyrrole (VII)

A mixture of Compound IV (2.68g, 0.01 mole) and o-phenylenediamine (1.08g, 0.01 mole) in ethanol (50 m*l*) was refluxed for two hours. The reaction mixture was cooled and the precipitated solid was collected by filtration and recrystallized from methanol to yield yellow crystals of VII (2.7g); IR (KBr): 1640 (C = N) & 1700 (C = O) and 3300 (NH_2) cm^1; ^{1}H-NMR (DMSO-d_6) δ : 2.10 (s, 3H, CH_3 at C_4), 2.15 (CH_3 at C_5) 3.55 (broad s, NH_2) 3.85, (s, 3H, OCH_3), 5.15 (s,2H,benzylic protons),6.75-7.85 (m, 9H, aromatic protons).

1-Benzyl-2,3,10-trimethylpyrrolo[2,3-d]pyrimidino[1, 6-a] benzimidazole (VII)

A mixture of pyrrolo [2, 3-d] oxain-4-one (IV) (2.68g, 0.01 mole) and o-phenylenediamine (1.08g, 0.01 mole) in acetic acid (25 m*l*) containing fused sodium acetate (1g) was refluxed for three hours. The reaction mixture was cooled and the precipitate solid was collected by filtration and recrystallized from acetic acid to afford a brown crystals (1.8g) of VIII; IR (KBr) 1640 (C = N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 2.1 (s, 3H, CH_3 at C_4), 2.15 (s, 3H, CH_3 at C_5), 2.25 (s, 3H, CH_3 at C_{10}), 5.25 (s, 2H, benzylic protons), 6.80-7.85 (m, 9H, aromatic protons).

Cyclization of VII

1-Benzyl-2-acetamido-3-(2-aminophenyl) carboxamido-4,5-dimethylpyrrole(VII) (3.79g, 0.01 mole) in glacial acetic acid (35 m*l*) containing fused sodium acetate (1g) was refluxed for two hours.

After cooling, the separated solid was collected by filtration and recrystallized from acetic acid to give VIII with same melting point and microanalytical data of the compound obtained from the above route.

3-Amino-7-benzyl-2,5,6-trimethylpyrrolo [2, 3-d] pyrimidin-4 (2H)-one (IX)

A solution of Compound IV (2.68g, 0.01 mole) and hydrazine hydrate 80% (3 m*l*) in acetic acid (50 m*l*) containing fused sodium acetate (1g) was refluxed for two hours. The separated solid was collected and recrystallized from acetic acid to give brown solid of IX (1.6g); IR (KBr) 1645 (C = N), 1715 (CONR) and 3300 (NH_2) cm^{-1}.

Reaction of 1-benzyl-2,5,6-trimethyl-3-(p-methoxyphenyl) pyrrolo-[2,3-d] pyrimidin-4-(2H)-one (VI) with phenacylbromide

A mixture of Compound VI (3.70g, 0.01 mole) and phenacyl bromide (1.99g, 0.01 mole) in methanol (50 m*l*) containing anhydrous potassium carbonate (3g) was refluxed for one hour. After cooling the reaction mixture to room temperature, alcoholic potassium hydroxide (3 m*l*) was added and the mixture was further refluxed for 2 hours. After standing overnight at the ambient temperature, the precipitated formed was collected by filtration and recrystallized from ethanol to give 1-benzzyl-2,3-dimethyl-5-(p-methoxyphenyl)-7-phenylpyrrolo [2, 3-d] pyrimidino [1, 2-a] pyrrole (IV) as reddish crystals (2.60g); IR (KBr) 1635 (-C = N) and 1720 (CONR) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ :2.40 (s, 6H, C_2 & C_3-CH_3), 5.10 (s, 2H, benzylic protons), 6.20 (s, 2H, olefinic pyrrole protons), 7.15-7.85 (m, 14H, aromatic protons).

Similarly, 1-benzyl-2, 3-dimethyl-5-(benzoylmethylamino)-7-phenyl-pyrrolo [2, 3-d] pyrimidino [1, 2-a] pyrrole (XI) was obtained as a yellow crystals in good yield; IR (KBr), 1635 (-C = N-) 1680 and 1720 (-CNR) and 3300 (NH); ^{1}H-NMR ($CDCl_3$) δ : 2.40 (s, 6H, C_2 & C_3-CH_3), 2.90 (d, 2H-$COCH_2$),5.15 (s, 2H, benzylic protons), 5.25 (broad s, 1H, NH), 6.20 (s, 2H, olefinic pyrrole protons), 7.3-8.0 (m, 15H, aromatic protons).

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