AN EFFICIENT SYNTHESIS OF SOME NOVEL 5,7-DIARYLPYRIDO[4,3-d]PYRIMIDINES

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The 4-oxo-N,2,6-triphenylpiperidine-3-carboxamides (**3a-f**) were synthesized using arylaldehydes, ammonium acetate and acetoacetanilide, which in turn converted into 5,6,7,8-tetrahydro-4-hydroxy-5,7-diarylpyrido[4,3-d]pyrimidin-2(3H)-ones (**4a-f**), 2-amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols (**5a-f**) by condensing with guanidine carbonate and urea respectively.

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Introduction

The piperidine ring is an ubiquitous structural feature of many alkaloid natural products and drug candidates. Watson et al. asserted that during a recent 10-year period there were thousands of piperidine compounds mentioned in clinical and preclinical studies.[1] Piperidones are somewhat less prominent, but often they serve a role as advanced intermediates prior to their conversion to piperidines. Reviews updating progress in the stereoselective syntheses of substituted piperidines have appeared recently.[2] One of the review presents synthetic methodologies on the basis of diversity and stereocontrol.[3]

Compounds with piperdin-4-one nucleus were reprted to have various important biological properties such as antiviral, anti-inflammatory, local anesthetic, anticancer, antimicrobial activity.[3-7] The piperidones were also reported to act as neurokinin receptor antagonists, analgesic and anti-hypertensive agents.[8-14] The importance of piperdin-4-one as intermediates in the synthesis of a diversity of compounds with potent physiological activity has been reviewed by Prostakov and Gaivoronskaya.[15] The studies undertaken on 4-piperidones have direct relation to the synthesis of drug molecules. The effect of substituent at second, third and sixth position particularly, aryl substituent at second and/or sixth positions with regard to its biological activity have been well documented. The preparation of pharmaceutically active compounds of this kind remains a major challenge in synthetic organic chemistry. Due to the demand for improved selectivity and reduction of side effects of potential drugs in pharmaceutical research, compounds with increasing molecular complexity. However, the biological properties of piperidines are highly dependent on the type and locations of substituent on the heterocyclic ring continue to drive the search for new methodologies. Similarly imidazole, oxazole and pyrazole were also exhibiting several activities and the fused bicycles of 4-piperidones with imidazole, pyrazole, oxazole and pyrimidine were expected to show intersting bio activites. In continuation of the earlier interest,[17] herein we report the synthesis of diarylpyrido[4,3-d]pyrimidine derivatives which are hitherto unrepored.

Experimental

Synthesis of compound 3a-f was done according to the procedure available in literature .[17]

General Procedure for the synthesis of (4a-f)

5,6,7,8-Tetrahydro-4-hydroxy-5,7-diarylpyrido[4,3-d]pyrimidin-2(3H)-ones (**4a-f**) are synthesized by the condensation of **3a-f** with urea in ethanol. A mixture of 4-piperidone (0.003246 mol,1.2 g) in ethanol and Urea (0.003246 mol, 0.2g) was refluxed on a water bath for 6 hr. The reaction mixture was cooled to room temperature; the solid product was washed with ethanol-ether (1:5). The product was recrystallized using ethanol. The purity of the product was checked through TLC and the melting point was recorded. The formation of the product was confirmed by the absence of carbonyl stretching frequency in IR spectrum which appeared in the piperidones. The yield and other physical parameters of **4a-f** are given in the Table-1.

General Procedure for the synthesis of (5a-f)

2-Amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols (**5a-f**) are synthesized by the condensation of **3a-f** with guanidine carbonate in ethanol. A mixture of (0.003246 mol, 1.2 g) of 4-piperidone in ethanol solution and 0.003246 mol, 0.4g of guanidine carbonate was refluxed on a water bath for 8 hr. The reaction mixture was cooled to room temperature; the obtained solid product was washed with mixture of ethanol-ether (1:5). The crude product was recrystallized using ethanol. The purity was checked through TLC and the melting point was observed in open capillaries. The formation of the product was confirmed by the absence of carbonyl peaks which appeared in the piperidones. The yield and other physical parameters are given in the Table 1 for all the compounds **5a-f**.

Spectral data of newly prepared compounds

4a: Yield (89 %), m.p = 175 °C. IR data in cm^{-1}: 3289 (NH str), 3167, 3068 (Aromatic str), 3452 (Aromatic OH str), 1653 (N-CO-N str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.90 (s, 1H), 1.51-1.70 (t, 2H), 2.51 (t, 1H), 3.30 (d, 1H), 3.70 (s, 1H), 4.0 (t, 1H), 5.35 (d, 1H), 7.27-7.32 (m, 6H), 7.45 (d, 4H), 8.0 (s, 1H). $C_{19}H_{19}N_3O_2$ (Calculated) C, 71.01; H, 5.96; N, 13.08; Found C, 71.21; H, 6.06; N, 12.88; GC-Mass Bass Peak = 92.

4b: Yield (86 %), m.p=220. IR data in cm^{-1}: 3265 (NH str), 3173, 3064 (Aromatic str), 3328 (Aromatic OH str), 1645 (N-CO-N str), 1573 (C-O-C str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.90 (s, 1H), 1.62-1.70 (t, 2H), 2.50 (t, 1H), 3.36 (d, 1H), 3.65 (s, 1H), 3.89 (s, 6H), 3.93 (t, 1H), 5.30 (d, 1H), 6.95(d, 4H), 7.20 (d, 4H), 8.0 (s, 1H). ES-MS: 381.17[M+]; $C_{21}H_{23}N_3O_4$ (Calculated): C, 66.13; H, 6.08; N, 11.02; Found: C, 66.33; H, 5.18; N, 11.01.

4c: Yield (88 %), m.p =217 °C. IR data in cm^{-1}: 3283 (NH str), 3376 (Aromatic OH str), 1639 (N-CO-N str), 1584 (C-O-C str), 3125 C-C str (furan). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.90 (s, 1H), 1.60-1.70 (t, 2H), 2.50 (t, 1H), 3.65 (s, 1H), 4.1 (t, 2H), 5.35 (d, 1H), 6.45-6.50 (m, 4H), 7.65 (d, 2H), 8.0 (s, 1H). $C_{15}H_{15}N_3O_4$ (Calculated): C, 59.79; H, 5.02; N, 13.95; O, 21.24; Found: C, 60.02; H, 4.05; N, 13.95; ES MS: 301.10.

4d: Yield (82 %), m.p = 192 °C. IR data in cm^{-1}: 3397 (NH str), 3251, 3192 (Aromatic str), 3459 (Aromatic OH str), 1669 (N-CO-N str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.90 (s, 1H), 1.62-1.70 (t, 2H), 2.50 (t, 1H), 3.36 (d, 1H), 3.65 (s, 1H), 3.89 (s, 6H), 3.93 (t, 1H), 5.30 (d, 1H), 6.95(d, 4H), 7.20 (d, 4H), 8.0 (s, 1H). $C_{19}H_{17}N_3O_2Cl_2$ (Calculated): C, 66.13; H, 6.08; N, 11.02; Found; C, 66.15; H, 6.88; N, 11.12; ES-MS: 381.

4e: Yield (84 %), m.p = 186 °C. IR data in cm^{-1}: 3386 (NH str), 3254, 3194 (Aromatic str), 3459 (Aromatic OH str), 1672 (N-CO-N str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.90 (s, 1H), 1.62-1.70 (t, 2H), 2.50 (t, 1H), 3.36 (d, 1H), 3.65 (s, 1H), 3.89 (s, 6H), 3.93 (t, 1H), 5.30 (d, 1H), 6.95(d, 4H), 7.20 (d, 4H), 8.0 (s, 1H).$C_{19}H_{17}N_3O_2Cl_2$ (Calculated): C, 66.13; H, 6.08; N, 11.02; Found; C, 65.93; H, 5.48; N, 11.06.

4f: Yield (82%), m.p = 192 °C. IR data in cm^{-1}: 3397 (NH str), 3251, 3192 (Aromatic str C-Cl str), 3459 (Aromatic OH str), 1669 (N-CO-N str), 694 (C-Cl str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.90 (s, 1H), 1.62-1.70 (t, 2H), 2.50 (t, 1H), 3.36 (d, 1H), 3.65 (s, 1H), 3.89 (s, 6H), 5.40 (s, 1H), 7.50-7.62 (m, 8H), 8.0 (s, 1H).$C_{19}H_{17}N_3O_2Cl_2$ (Calculated): C, 58.47; H, 4.39; Cl, 18.17; N, 10.77: Found; C, 58.40; H, 5.58; N, 10.01; ES-MS: 390.26; GC-Mass Base Peak = 138.

5a: Yield (80%), m.p =270 °C. IR data in cm^{-1}: 3250 (NH str), 3176, 3065 (Aromatic str), 3368 (Aromatic OH str), 1654 (C-N str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.90 (s, 1H), 2.80-2.98 (t, 2H), 4.30 (t, 1H), 5.23 (s, 1H), 7.0 (s, 2H), 7.28-7.40 (m, 10H), 11.0 (s, 1H). GC-Mass Base Peak = 187, $C_{19}H_{18}N_4O$; (Calculated) C, 71.68; H, 5.70; N, 17.60; Found: C, 71.81; H, 4.69; N, 16.78.

5b: Yield (75 %), m.p =258 °C. IR data in cm^{-1}: 3265 (NH str), 3271 (Aromatic str), 3043 (Aromatic OH str), 336 (C-N str), 1673, 1546 (C-O-C str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.93 (s, 1H), 2.80-3.03 (t, 2H), 3.83 (s, 6H), 4.30 (t, 1H), 5.18 (s, 1H), 6.87-6.97 (m, 6H), 7.15-7.21 (m, 4H), 11.0 (s, 1H). $C_{21}H_{22}N_4O_3$. (Calculated) C, 66.65; H, 5.86; N, 14.81; O, 12.68. Found C, 67.12; H, 5.86; N, 14.51.

5c: Yield (79 %), m.p =283 °C. IR data in cm^{-1}: 3226 (NH str), 3365 (Aromatic OH str), 1652 (C-N str), 3143 (C-C str furan). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.93 (s, 1H), 2.80-2.94 (t, 2H), 4.56 (t, 1H), 5.46 (s, 1H), 6.18 (d, 1H), 6.45-6.50 (m, 3H), 7.0 (s, 2H), 7.68(d, 2H), 11.0 (s, 1H).$C_{15}H_{14}N_4O_3$ (Calculated) C, 60.40; H, 4.73; N, 18.78; O, 16.09: Found C, 60.50; H, 3.76; N, 18.88.

5d: Yield (72 %), m.p =258 °C. IR data in cm^{-1}: NH str 3265, Aromatic str 3271, 3043, Aromatic OH str 336, C-N str 1673, C-O-C str 1546. ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.93 (s, 1H), 2.80-3.03 (t, 2H), 3.83 (s, 6H), 4.30 (t, 1H), 5.18 (s, 1H), 6.87-6.97 (m, 6H), 7.15-7.21 (m, 4H), 11.0 (s, 1H).$C_{21}H_{22}N_4O_3$(Calculated) C, 66.65; H, 5.86; N, 14.81; O, 12.68: Found C, 66.25; H, 4.16; N, 14.21.

5e: Yield (75 %), m.p =258 °C. IR data in cm^{-1}: NH str 3265, Aromatic str 3271, 3043, Aromatic OH str 336, C-N str 1673, C-O-C str 1546. ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.93 (s, 1H), 2.80-3.03 (t, 2H), 3.83 (s, 6H), 4.30 (t, 1H), 5.18 (s, 1H), 6.87-6.97 (m, 6H), 7.15-7.21 (m, 4H), 11.0 (s, 1H). $C_{21}H_{22}N_4O_3$(Calculated) C, 66.46; H, 5.66; N, 14.71: Found C, 66.61; H, 4.66; N, 13.71.

5f: Yield (68 %), m.p =292°C. IR data in cm^{-1}: 3278 (NH str), 3176, 3076 (Aromatic str), 342 (Aromatic OH str),1657 (C-N str), 694 (C-Cl str). ^{1}H-NMR (400MHz, $CDCl_3$): δ 1.93 (s, 1H), 2.80-3.0 (t, 2H), 4.30 (t, 1H), 5.20 (s, 1H), 7.0 (s, 2H), 7.20-7.24 (d, 2H), 7.41-7.50 (m, 6H), 11.0 (s, 1H).$C_{19}H_{16}N_4OCl_2$ Calculated C, 58.93; H, 4.16; Cl, 18.31; N, 14.47; O, 4.13: Found C, 58.83; H, 3.73; N, 14.40.

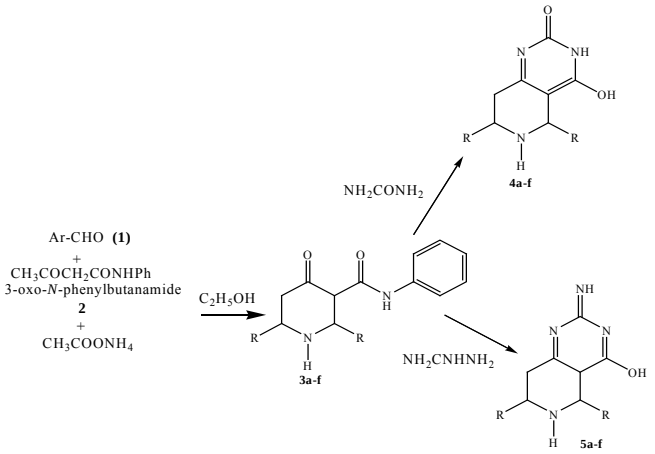
Results and Discussion

The 2, 6-diaryl-4-piperidones (**3a-f**) were synthesised by the procedure available in the literature.[17]

5,6,7,8-Tetrahydro-4-hydroxy-5,7-diarylpyrido[4,3-d]pyrimidin-2(3H)-ones (**4a-f**) are synthesized by the condensation of **3a-f** with urea in ethanol. A mixture of 4-piperidone (0.003246 mol, 1.2 g) in ethanol and urea (0.003246 mol, 0.2 g) was refluxed on a water bath for 6 hr. 2-Amino-5,6,7,8-tetrahydro-5,7-diarylpyrido[4,3-d]pyrimidin-4-ols (**5a-f**) were synthesized by the condensation of **3a-f** with guanidine carbonate in ethanol. A mixture of 0.003246 mol, (1.2 g) 4-piperidone in ethanol and 0.003246 mol (0.4 g) of guanidine carbonate was refluxed on a water bath for 8 h. The formation of desired products was confirmed by spectral data (included in experimental section).

Table 1. Physical data of the compounds (**4a-f**), (**5a-f**) and (**3a-f**)

S. No	R	M.P ºC	Yield, %
4a	Phenyl	175-78	79
4b	4-Methoxyphenyl	220-22	86
4c	Furfural	217-19	88
4d	3-Methoxyphenyl	217-20	88
4e	2-Methoxyphenyl	218-19	83
4f	4-Chlorophenyl	192-94	72
5a	Phenyl	270-72	80
5b	4-Methoxyphenyl	259-62	75
5c	Furfural	227-30	78
5d	3-Methoxyphenyl	258-60	75
5e	2-Methoxyphenyl	254-56	75
5f	4-Chlorophenyl	292-95	68



Scheme 1. Synthesis of diarylpyrido[4,3-d]pyrimidine derivatives

Conclusion

In conclusion, synthesis of some fused heterocycles with 4-piperidone moiety and 4,5,6,7-tetrahydro-4,6-diaryl-2*H*-pyrazolo[4,3-c]pyridin-3-ols, 4,5,6,7-tetrahydro-4,6-diaryl-2*H*-pyrazolo[4,3-c]pyridin-3-ols were attempted successfully, the compounds with fused pyrazole were proved as biologically important molecules. In the present work molecules with pyrazole moiety were obtained using a simple reaction protocol with moderate yield. The synthesized compounds were characterized by IR spectrum, GC-MS spectrum, ^{1}H NMR spectrum and elemental analysis.

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