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Synthesis of Some New Pyrazolo[3,4-*d*]pyrimidin-4-amines

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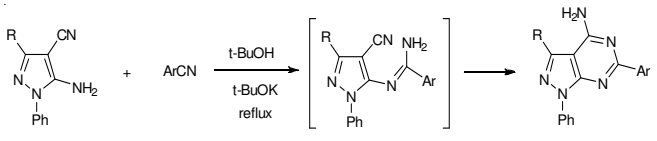
Some new derivatives of pyrazolo[3,4-*d*]pyrimidin-4-amines have been prepared through cyclocondensation reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitriles with aryl nitriles in the presence of potassium *t*-butoxide in boiling *t*-butanol.

Key Words: 5-Amino-1-phenyl-1*H*-pyrazole-4-carbonitriles, Aryl nitriles, Cyclocondensation, Pyrazolo[3,4-*d*]pyrimidin-4-amines.

INTRODUCTION

Pyrazolo[3,4-*d*]pyrimidins are a large group of heterocycles with diverse and interesting biological activities. These compounds are reported to possess significant vasodilatory[1], fungicidal[2,3], herbicidal[4-6] and antimicrobial[7-9] activities. A number of these compounds are also known to inhibit enzymes such as adenosine deaminase[10] and plasmodium falciparum PfPK7 protein kinase[11]. The routes to pyrazolo[3,4-*d*]pyrimidins mainly involve cyclocondensation of suitably functionalized pyrimidines or pyrazoles with different electrophiles and nucleophiles such as isocyanates[12], methylhydrazine in combination with aldehydes[13], thiophosgene in combination with amines[14], allylamine, ammonium and ethylenediamine[15] and orthoesters[16].

In pursuing these studies and due to our interest in the synthesis of heterocyclic compounds with potential biological activities[17-32], in this paper we wish to report a convenient synthesis of new pyrazolo[3,4-*d*]pyrimidins **3a-f** in synthetically useful yields by reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitriles **1a-c**[21] with aryl nitriles **2a-c** in the presence of potassium *t*-butoxide in boiling *t*-butanol (**Scheme-I**).



1a-c **2a-c** **I** **3a-f**

1a: R = H
1b: R = Me
1c: R = Et
2a: Ar = 4-BrC_6H_4
2b: Ar = 4-ClC_6H_4
2c: Ar = 3-MeC_6H_4
3a: R = H, Ar = 4-BrC_6H_4
3b: R = H, Ar = 4-ClC_6H_4
3c: R = Me, Ar = 4-ClC_6H_4
3d: R = Et, Ar = 4-ClC_6H_4
3e: R = H, Ar = 3-MeC_6H_4
3f: R = Me, Ar = 3-MeC_6H_4

Scheme-I: Synthesis of pyrazolo[3,4-*d*]pyrimidin-4-amines

EXPERIMENTAL

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Elemental analysis was performed on a thermo finnigan flash EA microanalyzer.

General procedure for the synthesis of pyrazolo[3,4-*d*]pyrimidin-4-amines (3a-f): To a solution of the 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitriles **1a-c** (5 mmol) and potassium *t*-butoxide (1 mmol) in *t*-butanol (30 mL), aryl nitriles **2a-c** (6 mmol) was added. The reaction mixture was heated under reflux for 4-7 h. The progress of the reaction was monitored by TLC. Upon completion, the solvent was evaporated *in vacuo*, the residue was dissolved in water (20 mL) and subsequently neutralized by 1N HCl. The crude product was collected and recrystallized from ethanol to give compounds **3a-f** in 72-87 % yields.

6-(4-Bromophenyl)-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (3a): ^{1}H NMR (DMSO-d_6) δ: 7.35-7.85 (m, 5H, arom-H), 8.10 (br, 2H, NH_2), 8.30-8.50 (m, 5H, arom-H); IR, (KBr, ν_{max}, cm^{-1}): 3294 and 3161 (NH_2); Anal. calcd for $C_{17}H_{12}N_5Br$: C, 55.75; H, 3.30; N, 19.12. Found: C, 55.44; H, 3.49; N, 19.56.

6-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (3b): ^{1}H NMR (DMSO-d_6) δ: 7.30-7.75 (m, 5H, arom-H), 7.98 (s.br, 2H, NH_2), 8.15-8.50 (m, 5H, arom-H); IR, (KBr, ν_{max}, cm^{-1}): 3307 and 3153 (NH_2); Anal. calcd. for $C_{17}H_{12}N_5Cl$: C, 63.46; H, 3.76; N, 21.77. Found: C, 63.21; H, 3.57; N, 22.38.

6-(4-Chlorophenyl)-3-methyl-1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidin-4-amine (3c): ^{1}H NMR (DMSO-d_6) δ: 2.64

(s, 3H, CH_3), 7.25-7.80 (m, 7H, arom-H and NH_2), 8.20-8.60 (m, 4H, arom-H); IR, (KBr, ν_{max}, cm^{-1}): 3287 and 3169 (NH_2); Anal. calcd. for $C_{18}H_{14}N_5Cl$: C, 64.38; H, 4.20; N, 20.86. Found: C, 64.76; H, 3.98; N, 20.53.

6-(4-Chlorophenyl)-3-ethyl-1-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (3d): ^{1}H NMR (DMSO-d_6) δ: 1.32 (t, 3H, CH_3), 3.12 (q, 2H, CH_2), 7.25-7.75 (m, 7H, arom-H and NH_2), 8.25-8.60 (m, 4H, arom-H); IR, (KBr, ν_{max}, cm^{-1}): 3315 and 3174 (NH_2); Anal. calcd for $C_{19}H_{16}N_5Cl$: C, 65.24; H, 4.61; N, 20.02. Found: C, 65.01; H, 4.86; N, 19.79.

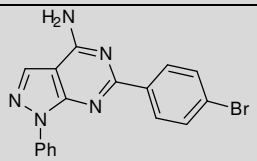
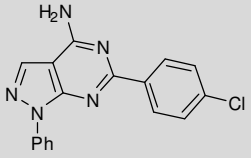
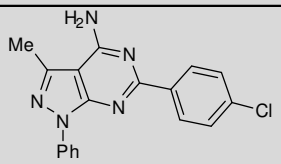
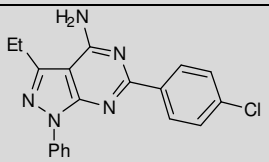
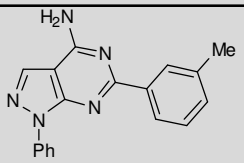
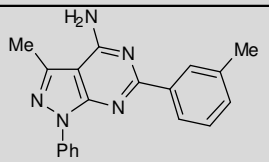
6-(3-Methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-d]-pyrimidin-4-amine (3e): ^{1}H NMR (DMSO-d_6) δ: 2.43 (s, 3H, CH_3), 7.25-7.80 (m, 6H, arom-H), 8.05-8.40 (m, 5H, arom-H and NH_2), 8.64 (s, 1H, CH of pyrazole); IR, (KBr, ν_{max}, cm^{-1}): 3212 and 3147 (NH_2) cm^{-1}; Anal. calcd for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 72.43; H, 5.11; N, 23.08.

3-Methyl-6-(3-methylphenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidin-4-amine (3f): ^{1}H NMR (DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.20-7.80 (m, 7H, arom-H and NH_2), 8.15-8.45 (m, 4H, arom-H); IR, (KBr, ν_{max}, cm^{-1}): 3348 and 3170 (NH_2); Anal. calcd for $C_{19}H_{17}N_5$: C, 72.36; H, 5.43; N, 22.21. Found: C, 72.68; H, 5.25; N, 22.03.

RESULTS AND DISCUSSION

Cyclocondensation of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitriles (**1a-c**) with aryl nitriles (**2a-c**) in the presence of potassium *t*-butoxide in *t*-butanol under reflux gave products identified as pyrazolo[3,4-*d*]pyrimidin-4-amines (**3a-f**) (Table-1). The structure of new compounds **3a-f** was deduced from their spectral and microanalytical data. For example, the ^{1}H NMR spectrum of **3b** in d_6-DMSO did not show the NH_2 signal at δ 4.72 ppm belonging to the precurser **1a**, but instead showed a broad 2*H* signal at δ 7.98 ppm for NH_2 group as well as two multiplet at δ 7.30-7.75 and 8.15-8.50 ppm belonging to the aromatic rings indicating the formation of the compound **3b**. The IR spectrum was devoid of the CN absorption band at

TABLE-1
SYNTHESIS OF PYRAZOLO[3,4-*d*]PYRIMIDIN-4-AMINES **3a-f**[a]

Entry	R	Ar	Products	Time (h)	Yields (%)[b]	m.p. (ºC)
1	H	4-BrC_6H_4	 **3a**	6	72	200-202
2	H	4-ClC_6H_4	 **3b**	5	81	209-211
3	Me	4-ClC_6H_4	 **3c**	6	77	194-195
4	Et	4-ClC_6H_4	 **3d**	6	81	190-192
5	H	3-MeC_6H_4	 **3e**	4	87	198-200
6	Me	3-MeC_6H_4	 **3f**	7	78	166-168

[a]5-amino-1-phenyl-1*H*-pyrazole-4-carbonitriles (**1a-c**) (5 mmol) and aryl nitriles (**2a-c**) (6 mmol) in the presence of potassium *t*-butoxide (1 mmol) in boiling *t*-butanol (30 mL); [b]Isolated yields

2202 cm^{-1} of the precursor, which shows the inclusion of nitrile moiety in cyclocondensation process. Also this compound gave satisfactory elemental analysis data corresponding to the molecular formula $C_{17}H_{12}N_5Cl$. The formation of the products **3a-f** was assumed to proceed *via* the intermediates **[I]**. However, under these conditions, attempts to isolate the intermediates **[I]** failed when we carefully monitored the reactions.

Conclusion

In conclusion, we have reported a facile synthesis of some new pyrazolo[3,4-*d*]pyrimidin-4-amines in good yields by cyclocondensation reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitriles with aryl nitriles in the presence of potassium *t*-butoxide in boiling *t*-butanol.

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REFERENCES

1. P. Gong, Y.F. Zhao and D. Wang, *Chin. Chem. Lett.*, **13**, 613 (2002).
2. H.Q. Wang, W.P. Zhou, Y.Y. Wang and C.R. Lin, *J. Agric. Food Chem.*, **56**, 7321 (2008).
3. U. Gupta, V. Sareen, V. Khatri and S. Chugh, *Indian J. Heterocycl. Chem.*, **15**, 305 (2006).
4. H.Q. Wang, H. Liu and Z.J. Liu, *Chin. J. Org. Chem.*, **24**, 1563 (2004).
5. H. Liu, H.Q. Wang, M.W. Ding, Z.J. Liu and W.J. Xiao, *J. Fluorine Chem.*, **127**, 1584 (2006).
6. H. Liu, H.Q. Wang and Z.H. Liu, *Bioorg. Med. Chem. Lett.*, **17**, 2203 (2007).
7. C.N. Khobragade, R.G. Bodade, S.G. Konda, B.S. Dawane and A.V. Manwar, *Eur. J. Med. Chem.*, **45**, 1635 (2010).
8. R. Perumal, E. Jayachandran, L.V.G. Naragund, B. Shivakumar, B.H.M.J. Swamy and G.M. Srinivasa, *J. Heterocycl. Chem.*, **15**, 413 (2006).
9. S.M. Hassan, H.A. Emam and M.M. Abdelall, *Phosphorus, Sulfur, Silicon Rel. Elem.*, **175**, 109 (2001).
10. C. La Motta, S. Sartini, L. Mugnaini, S. Salerno, F. Simorini, S. Taliani, A.M. Marini, F. Da Settinio, A. Lavecchia, E. Novellino, L. Antonioli, M. Fornai, C. Blandizzi and M. Del Tacca, *J. Med. Chem.*, **52**, 1681 (2009).
11. M. Klein, P. Diner, D. Dorin-Semblat, C. Doerig and M. Grotli, *Org. Biomol. Chem.*, **7**, 3421 (2009).
12. P.J. Bhuyan, H.N. Borah and J.S. Sandhu, *Tetrahedron Lett.*, **43**, 895 (2002).
13. R. Neidlein and Z.J. Wang, *Heterocycles*, **45**, 1509 (1997).
14. F. Oertel, D. Vogel and P.H. Richter, *Pharmazie*, **47**, 251 (1992).
15. W.Q. Chen and G.Y. Jin, *Phosphorus Sulfur, Silicon Rel. Elem.*, **177**, 1193 (2002).
16. A. Davoodnia, M. Rahimizadeh, Sh. Rivadeh, M. Bakavoli and M. Roshani, *Indian J. Heterocyl. Chem.*, **16**, 151 (2006).
17. M. Bakavoli, A. Davoodnia, M. Rahimizadeh and M.M. Heravi, *Mendeleev Commun.*, **16**, 29 (2006).
18. A. Davoodnia, M. Bakavoli, A. Vahedinia, M. Rahimizadeh and M. Roshani, *Heterocycles*, **68**, 801 (2006).
19. A. Davoodnia, H. Behmadi, A. Zare-Bidaki, M. Bakavoli and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, **18**, 1163 (2007).
20. A. Davoodnia, M. Bakavoli, Gh. Barakouhi and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, **18**, 1483 (2007).
21. A. Davoodnia, R. Zhiani, M. Roshani, M. Bakavoli and M. Bashash *Phosphorus, Sulfur, Silicon Rel. Elem.,* **182**, 1219 (2007).
22. A. Davoodnia, M. Bakavoli, M. Bashash, M. Roshani and R. Zhiani, *Turk. J. Chem.*, **31**, 599 (2007).
23. A. Davoodnia, M. Bakavoli, Sh. Mohseni and N. Tavakoli-Hoseini, *Monatsh. Chem.*, **139**, 963 (2008).
24. A. Davoodnia, R. Zhiani and N. Tavakoli-Hoseini, *Monatsh. Chem.*, **139**, 1405 (2008).
25. A. Davoodnia, H. Eshghi, A. Salavaty and N. Tavakoli-Hoseini, *J. Chem. Res.*, **1**, 1 (2008).
26. A. Davoodnia, M. Bakavoli, N. Zareei and N. Tavakoli-Hoseini, *Bulg. Chem. Commun.*, **41**, 226 (2009).
27. A. Davoodnia, M. Bakavoli, M. Soleimany and N. Tavakoli-Hoseini, *Monatsh. Chem.*, **140**, 355 (2009).
28. A. Davoodnia, M. Rahimizadeh, H. Atapour-Mashhad and N. Tavakoli-Hoseini, *Heteroatom Chem.*, **20**, 346 (2009).
29. A. Davoodnia, M. Bakavoli, R. Moloudi, M. Khashi and N. Tavakoli-Hoseini, *Chin. Chem. Lett.*, **21**, 1 (2010).
30. A. Davoodnia, L. Anvari and N. Tavakoli-Hoseini, *Asian J. Chem.*, **23**, 3683 (2011).
31. A. Davoodnia, M. Kosari and N. Tavakoli-Hoseini, *Asian J. Chem.*, **23**, 3654 (2011).
32. A. Davoodnia, Sh. Ameli and N. Tavakoli-Hoseini, *Asian J. Chem.*, **23**, 3707 (2011).