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Synthesis and characterization of 9-methyl-2-morpholin-4-yl-8-substituted phenyl-1*H*-purine derivatives using polyphosphoric acid (PPA) as an efficient catalyst

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ABSTRACT

We demonstrate the synthesis of various purine derivatives through the coupling of N^4-methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine with various aldehydes by using polyphosphoric acid (PPA) as an efficient catalyst in DMF at reflux temperature. The PPA catalyst gave better yields (70–85%) in short reaction times (45–60 min). This commercially available cheap catalyst is more active than many reported expensive catalysts. Many aldehydes underwent the above conversion to form a series of 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purines.

The purines, including substituted purines and their tautomers are the most widely distributed as nitrogen-containing heterocycles in nature. Some, as components of nucleic acids and coenzymes, play vital roles in the genetic and metabolic processes of all living organisms. The purine bases, adenine and guanine together with pyrimidines, are fundamental components of all nucleic acids. Purine-related compounds have been investigated as potential chemotherapeutic agents. In particular, 6-mercaptopurine in the form of its nucleoside phosphate, inhibits several enzymes required for the synthesis of adenosine and guanosine nucleotides, and thus proves useful in selectively arresting the growth of tumors. The pyrazolopyrimidine has been used in gout therapy Emil Fischer, nobel laureate in chemistry in 1902, attributed the name purine to the fused imidazo [4,5-*d*] pyrimidine compound in 1884 and achieved its synthesis in 1898.[1] He further showed through a series of elegant transformations that the natural substances adenine, xanthine, caffeine, uric acid, and guanine correspond to different hydroxyl and amino derivatives of this fundamental system.[2] Purines bearing functionality at one or more of the seven peripheral atoms which make up its bicyclic structure can be readily synthesized by well-established routes from monocyclic precursors.[3] In order to gain further insight into the structural requirements for active antimycobacterial purines, we needed easy access to 9-arylpurines. Polyfunctionalized purines substituted at the 2, 6 and 8 positions are also obtained through the reaction of suitably activated purine intermediates with heteroatom and carbon nucleophiles through SNAr-type substitution and transition metal catalyzed coupling reactions.[4–15] *N*-Alkylation/acylation or Vorbruggen[16–18] and other electrophile based reactions, can also be used to introduce functionality onto the nitrogen atoms in the purine ring. An example of this methodology is the highly selective *N*-9 alkylation of purines under Mitsunobu conditions.[11,15,19,20] Purine derivatives acting as interferon inducers,[21–23] inhibitors of Hsp90,[24,25] antimycobacterial purines,[27–30] inhibitors of leukotriene A4 hydrolase,[31] sulfotransferase inhibitors,[32,33] Src tyrosine kinase inhibition,[34,35] P38αMAP kinase inhibitors,[36–38] inhibitors of inositol-1,4,5-trisphosphate-3-kinase[39] and cyclin-dependent kinase inhibitors.[40] In addition to the above, purines are also involved in many metabolic processes as cofactors associated with a great number of enzymes and receptors, notably ATP, GTP, GDP, cAMP, cGMP, AcCoA, NAD, NADP, FAD, PAPS and SAM,[41,42] which play key roles at different phases of the cell cycle, in cell signalling and other fundamental biological processes.[43] Indeed, a great variety of di, tri, or tetrasubstituted purines described in the literature have been found to be potent inhibitors. This wide range of biological activities

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displayed by purines is conferred by a judicious choice of the nature of the substituents that can be combined on the N-1, C-2, N-3, C-6, N-7, C-8 and N-9 centers. With such an easy access to so much structural diversity, the purine core has become a privileged structure in medicinal chemistry,[44] and an important scaffold in the preparation of combinatorial libraries. In general, two strategies are applied for the preparation of purine libraries. In the first procedure, a preformed purine ring loaded with various reactive functionalities is directly modified, which allows good regiocontrol at C-2, C-6, C-8, and N-9. Alternatively, substituted pyrimidine or imidazole precursors are functionalised, generating the second heterocycle of the purine core in the process with better region control at N-1, N-3, N-7, and N-9. Recently the synthesis of several purine derivatives like 6-aminopurines,[45] 6-amidopurines,[46] 9-substituted purines,[47] Michael addition of adenine,[48] arylation at N-9 of purines,[49]xanthine derivatives from 6-aminouracils,[50] and N-1 (or N-3) mono substituted 5,6-diaminouracil[51] pyrimidine precursors of 2,6,8,9-tetrasubstituted purines,[52] 8,9-disubstituted adenines,[53]2,8,9-trisubstituted adenine inhibitors of HSP90,[26] 6,7,8-trisubstituted purines[54], N-9-substituted 2,8-diaminopurines[55] and 2-(*N*-benzylpyrrolyl)-benzimidazoles using PPA[56] are reported. Here in the present work we wish to report the synthesis of various purine derivatives using simple polyphosphoric acid (PPA) as catalyst.

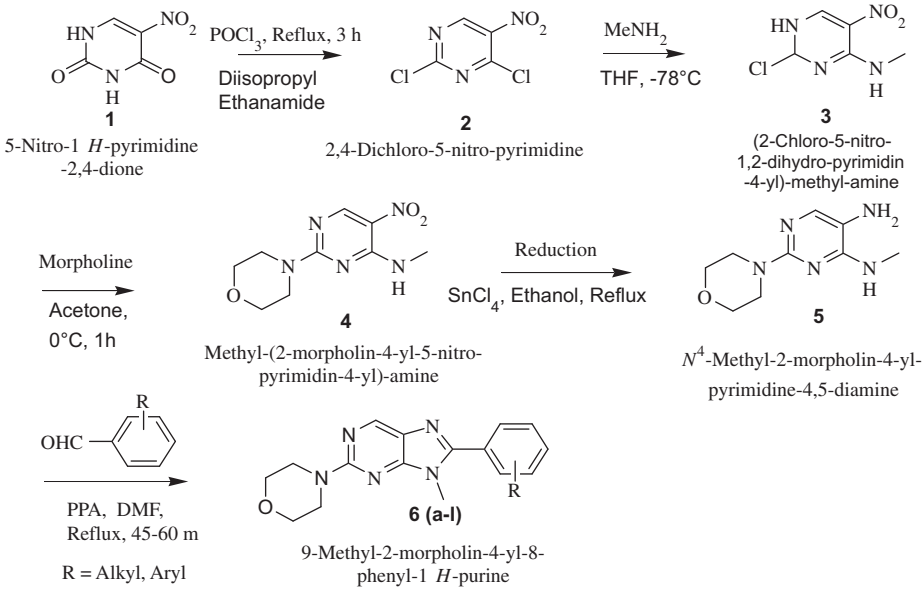
In continuation of the development of useful synthetic methodologies, initially, we have attempted the condensation of N^4-methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine **5** (1.0 mmol) with benzaldehyde (1.2 mmol) at reflux temperature in dimethyl formamide (DMF) solvent (5 ml) under nitrogen atmosphere, using polyphosphoric acid (1.5 equiv) as catalyst. The mixture was stirred at reflux temperature for about 1 h and afforded 82% yield of **6a**.

N^4-Methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine **5** is used as starting material for our scheme, which can be prepared from the 5-nitro uracil **1** by series of known synthetic reactions. 5-Nitro-1*H*-pyrimidine-2,4-dione (5-nitro uracil) **1** can be prepared by using uracil upon treatment with fuming nitric acid and H_2SO_4. 5-Nitro-1*H*-pyrimidine-2,4-dione (5-nitro uracil) on treatment with of phosphorous oxychloride and diisopropyl ethylamine will give 2,4-dichloro-5-nitropyrimidine **2** which was further used without purification. As per the Scheme 1, various reagents have been used to achieve the starting material **5**. Polyphosphoric acid (PPA) is a powerful dehydrating agent. This can also be used as ring closing reagent, reaction medium and solvent, spinning solvent. It has been used mainly as a ring closing reagent but its scope has not been fully explored. Here it has been applied for oxidative dehydrogenation of the cyclic intermediates formed from the condensation of N^4-methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine **5** and substituted aldehydes. Here, we have studied that purine derivatives **6(a–l)** can be synthesized[57] efficiently by treatment of N^4-methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine **5** with substituted aldehydes using polyphosphoric acid (PPA) and DMF as the solvent at reflux temperature. Several aromatic, heteroaromatic and aliphatic aldehydes underwent the above conversion to form a series of 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purines **6(a–l)**. Aromatic aldehydes containing both electron-donating and electron-withdrawing groups worked well along with the heteroaryl substituted aldehydes. Purine derivatives can be synthesized efficiently by treatment of N^4-methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine with aldehydes using PPA as an efficient ring closing reagent at room temperature. Similarly, different solvents were tested for the synthesis of 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purines **6a**. The reaction in dichloro methane (DCM), tetrahydrofuran (THF) gave the corresponding 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purines in low yield and also required prolonged reaction times (entries 1 and 2), whereas the reaction in methanol (MeOH), dimethoxy ethane (DME), acetonitrile (ACN) has resulted in slightly improved yields of the products (entries 3–5). However, the reaction in DMF gave 82% of the corresponding 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purines **6a** in 1 h, as can be seen from the Table 1.

Table 1
Effect of various solvents on the synthesis of purine derivative **6a** using PPA[a]

Entry	Solvent	Time (h)	Yield (%)
1	CH_2Cl_2	2	55
2	THF	2	58
3	CH_3OH	2	65
4	DME	1	60
5	CH_3CN	1	62
6	H_2O	2	30
7	DMF	1	82

[a] Reaction conditions: N^4-methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine (1 equiv), benzaldehyde (1.2 equiv), PPA (1.5 equiv), solvent (5 ml), reflux temperature.

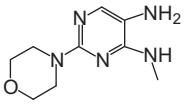
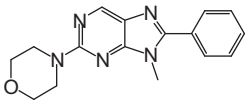
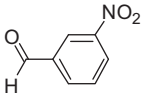
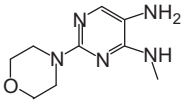
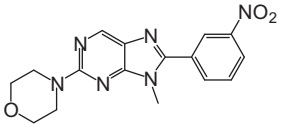
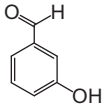
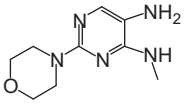
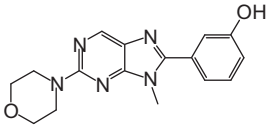
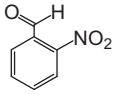
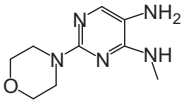
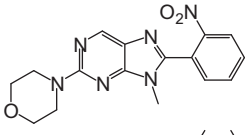
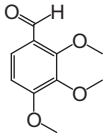
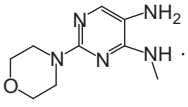
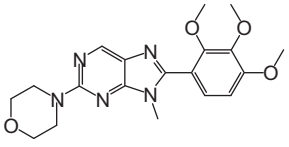
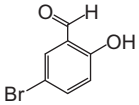
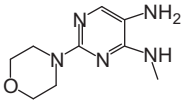
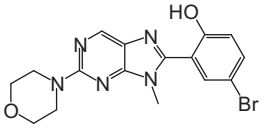
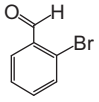
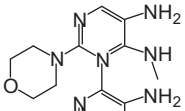
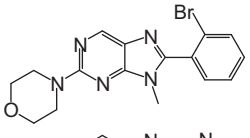
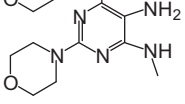
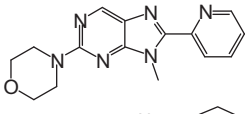
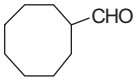
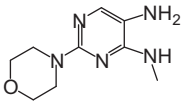
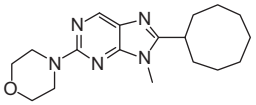
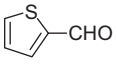
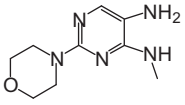
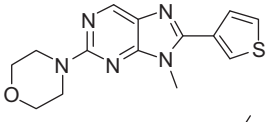
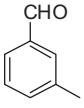
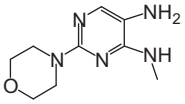
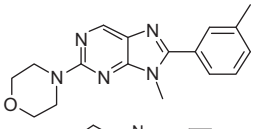
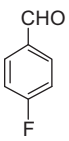
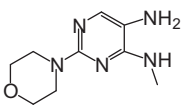
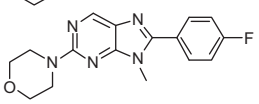


Scheme 1. Synthesis of purine derivatives using PPA.

The method is suitable for the preparation of 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purines from an acid sensitive aldehyde such as furfuraldehyde and the sterically hindered aldehyde, 2,3,4-trimethoxybenzaldehyde. The reaction conditions are mild and the experimental procedure is simple. The products were formed (Table 2) in high yields (70–85%) in 45–60 m. The structures of the products were determined from their spectral (IR, 1H NMR and MS) data.

The present work reveals that the synthesis of purine derivatives using PPA mediated condensation methodology. In continuation of the development of useful synthetic methodologies, we have observed that purine derivatives can be synthesized

Table 2
Synthesis of various 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purine derivatives **6**(**a–l**)

S.no.	Aldehyde	Diamine (**5**)	Product **6**(**a–l**)[a]	Time (min)	Yield[b] (%)
a				60	82
b				45	85
c				50	84
d				50	84
e				45	71
f				45	83
g				50	70
h				50	80
i				45	82
j				50	72
k				50	84
l				50	72

[a] All products were characterized by IR, NMR, and mass spectroscopy.
[b] Yield refers to pure products after purification by column chromatography.

efficiently by treatment of N^4-methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine with aldehydes using polyphosphoric acid (PPA) and DMF as the solvent at reflux temperature. N^4-Methyl-2-morpholin-4-yl-pyrimidine-4,5-diamine is used as starting material for our scheme, which can be prepared from the uracil by five known synthetic reactions. The reaction conditions are mild and the experimental procedure is simple. Further interdisciplinary studies are now under way searching for other novel types of biologically active compounds. Several types of compounds have found use in chemical biology and bioanalysis. The methodology of the condensation reactions on purines and nucleosides is now widely used in many laboratories and also the new cytostatic and antiviral compounds are inspiring further design of new compounds with potential biological activity.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.076.

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57. *Experimental*: Synthesis of 9-methyl-2-morpholin-4-yl-8-phenyl-9*H*-purine derivatives (**6**(**a–l**)): To the mixture of 2-morpholin-4-yl-pyrimidine-4,5-diamine (**1** equiv) and aldehyde (l.2 equiv) in DMF (5 ml) under N_2 atmosphere, PPA (1.5 equiv) was added. The mixture was stirred at reflux temperature for about 45–60 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured in ice cold water. The precipitate formed was filtered and dried to afford the desired product as off white or pale yellow solid (yield: ~70–85%). All compounds were confirmed by I.R, NMR, Mass and representative compound spectral data was given below and other compounds data was given in Supplementary data. **6l**: 8-(4-fluorophenyl)-9-methyl-2-morpholin-4-yl-9*H*-purine(Table 2): White solid; mp: 134–136 °C; IR (KBr): 3435.27, 2854.94, 1615.73, 1112.48 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.65–3.85 (m, 8H), 3.88 (s, 3H), 7.42 (t, J = 7.2 Hz, 2H), 7.98 (t, J = 7.4 Hz, 2H), 8.79 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.69, 161.40, 155.44, 154.69, 151.40, 147.99, 131.30, 131.18, 126.86, 126.14, 125.20, 115.96, 115.67, 65.00, 44.66, 29.94 ppm; m/z: 314.17(M^+).