ISSN: 0974 - 7516 Volume 8 Issue 2

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Short Communication

OCAIJ, 8(2), 2012 [57-59]

Simple, one-pot, three-component: Synthesis of tetrasubstituted pyrimidines under solvent-free conditions

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Received: 29th May, 2011 ; Accepted: 29th June, 2011

ABSTRACT

Tetrasubstituted pyrimidines are synthesized via a simple, one-pot, tree-component reaction between aromatic nitriles, hydroxylamine, and arylidenemalonitrile under solvent-free conditions in good to excellent yields.

KEYWORDS

Tetrasubstituted pyrimidines;
Tree-component reactions;
Solvent-free synthesis;
One-pot.

INTRODUCTION

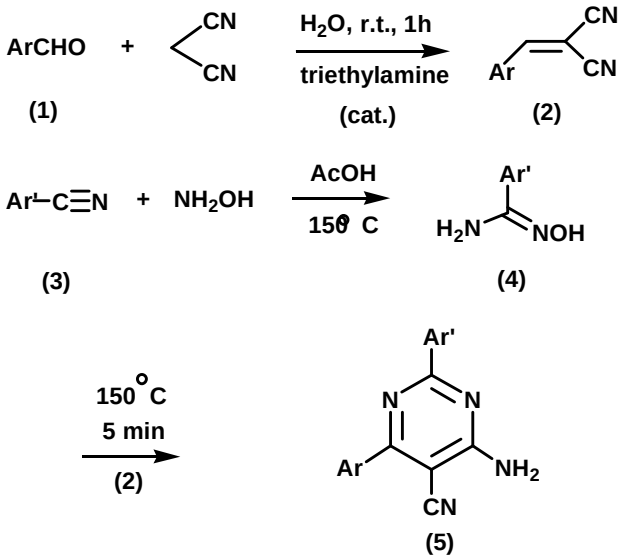
Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products have received a great deal of attention in organic and medicinal chemistry[1]. Pyrimidines are of chemical and pharmacological interest[2,3]. Derivatives containing pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial, and anticonvulsant activities[2-6]. Some examples are valuable drugs in treatment of hyperthyroidism, acute leukemis of childhood, and adult granulocytic leukemia[2]. 4-amino-5-pyrimidinecarbonitrile has been used as a kit for the detection of l-arginine (a substrate for nitric oxide synthases and a precursor of nitric oxid) and its derivatives in body samples[7], conjugated molecules which have a pyrimidine core as the key unit have recently recived much attention and they are prospective candidates for light-emitting devices[8] and molecular wires[9]. Tetrasubstituted pyrimidines have been synthesized using various methods and procedures including condensation of 1,2,3-trisubstituted enones with guanidies[10], reaction between 1,3-dicarbonyl compounds and N,N,N-tris(trimethylsilyl) amidines (a modification of the pinner pyrimidine synthesis)[11], four-component coupling reactin between 1,3-dicarbonyl compounds and N,N,N-tris(trimethylsilyl) amidines (a modification of the pinner pyrimidine synthesis)[11], reaction between *in situ* generated α,β-unsaturated imines and amidine or guanidine deraivatives[12].

Due to the unique properties of pyrimidine derivatives, developments of synthetic methods which enable facile access to this heterocycle are desirable. As part of our continuing efforts on the development of efficient methods for the preparation of widely used organic compounds from readily available building blocks, we describe here a simple, one pot, tree-component sysnthesis of tetrasubstituted pyrimidines under solvent-free conditions using raw materials, where possible to adapting the principles of green chemistry in order to reducing the use of organic solvent as potentially toxic and hazardous materials, as well as its simplicity and mild conditions, and inherent lower costs, with more likely industrial application[13]. Thus, aromatic nitriles **(3)**, hydroxylamine, arylidenemalononitrile **(2)** undergo a

one-pot tree-component reaction under solvent-free conditions and to produce tetrasubstituted pyrimidines **(5a-f)** in 86-95% yields (TABLE 1).

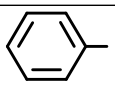
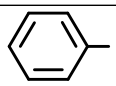
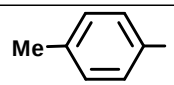
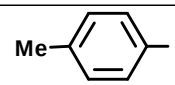
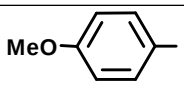
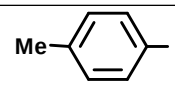
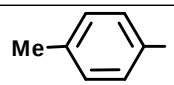
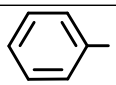
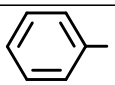
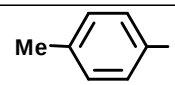
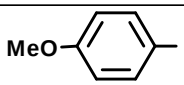
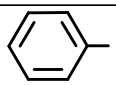
EXPERIMENTAL

The reaction were carried out by first mixing the nitrile **(3)** and hydroxylamine, proceeding in the presence of a catalytic amount of acetic acid under solvent-free condition at 150 °C for 3 minutes. After nearly complete Conversion to the corresponding amidoxime 4, as indicated by TLC monitoring, The arylidenemalononitrile **(2)** (which synthesized by reaction between the aldehyde **(1)** and malononitrile in water solution at room temperature with catalytic amount of triethylamine) were added to the reaction mixture and stirred for 5 minutes at 150 °C. TLC and ^{1}H NMR analysis of the reaction mixture clearly indicated formation of the corresponding 2,4,5,6-tetrasubstituted pyrimidines **(5a-f)** in 86-95% yields (TABLE 1). The structures of the isolated products were corroborated by the comparison of their m.p. values and their spectral data (high-field ^{1}H and ^{13}C NMR spectra) with those of authentic samples.



Scheme 1

TABLE 1

5	Ar	Ar'	% Yield	m.p. C
a			91	153-155
b			90	145-147
c			87	134-136
d			88	168-170
e			95	173-174
f			86	134-136

ACKNOWLEDGEMENT

This research was financially supported by Young Researchers Club of Takestan Branch, Islamic Azad University Takestan, Iran.

CONCLUSION

In conclusion, we have developed a simple, one-pot, tree-component, and solvent-free procedure for the preparation of 2,4,6-triarylpyrimidines of potential synthetic and pharmacological interest. Using raw materials, one-pot and solvent-free condition are the main advantages of this method. This method appears to have broad scope with respect to variation in the pyrimidines 2-,4-, and 6-positions and presents a straightforward procedure for the synthesis of 2,4,6-triarylpyrimidines.

4-amino-2,6-diphenyl-5-pyrimidinecarbonitrile (5a)

Colorless crystals. ^{1}H NMR (500.1 MHz, DMSO – d_6): δ 5.74 (2H, br. s, NH_2), 7.40-7.60 (6H, m, 6 CH), 8.13 (2 H, d, J = 7.7 Hz, 2 CH), 8.51 (2 H, d, J = 7.2 Hz, 2 CH). ^{13}C NMR (125.8 MHz, DMSO - d_6): δ 85.77 (CN), 117.11 (C), 129.08, 129.29, 129.39, 129.63, 131.97, and 132.39(6 CH), 136.93 and 137.17 (2 C), 165.36, 165.94, and 168.71 (3 C-N).

4-amini-2,6-bis(4-methylphenyl)-5-pyrimidinecarbonitrile (5b)

Colorless crystals. ^{1}H NMR (300.1 MHz, DMSO - d_6): δ 2.36 (3 H, s, CH_3), 7.31 (2 H, d, J = 8.0 Hz, 2 CH), 7.52-7.59 (3 H, m, 3 CH), 7.82-8.05 (2 H, br. s, NH_2), 7.96 (2 H, d, J = 7.6 Hz, 2 CH), 8.29 (2 H, d, J = 8.1 Hz, 2 CH). ^{13}C NMR (75.5 MHz, DMSO - d_6): δ 20.97 and 21.05 (2 CH_3), 83.74 (CN), 116.64 (C), 128.45, 128.56, 129.02 and 129.09 (4 CH),

133.86, 133.98, 140.93 and 141.51 (4 C), 163.99, 164.69 and 167.83 (3 C-N).

4-amino-6-(4-methoxyphenyl)-2-(4-methylphenyl)-5-pyrimidinecarbonitrile (5c)

Colorless crystals. ^{1}H NMR (300.1 MHz, DMSO - d_6): δ 2.36 (3 H, s, CH_3), 3.84(3 H, s, OCH3),7.11 (2 H, d, J = 8.6 Hz, 2 CH), 7.30 (2 H, d, J = 7.9 Hz, 2 CH), 7.63-8.00 (2 H, br. s, NH_2), 8.01 (2 H, d, J = 8.6 Hz, 2 CH), 8.29 (2 H, d, J = 7.9 Hz, 2 CH). ^{13}C NMR (75.5 MHz, DMSO - d_6): δ 21.12 (CH_3),55.42 (OCH_3), 83.10 (CN), 113.87 (CH), 116.91 (C), 128.44 (CH), 128.80 (C), 129.09 and 130.39 (2 CH), 134.03 and 141.45 (2 C), 161.54 (C-O), 163.86, 164.78 and 167.11 (3 C-N).

4-amino-6-(4-methylphenyl)-2-phenly-5-pyrimidinecarbonitrile (5d)

Colorless crystals. ^{1}H NMR (300.1 MHz, DMSO - d_6): δ 2.39 (3 H, s, CH_3), 7.36 (2 H, d, J = 8.1 Hz, 2 CH), 7.45-7.54 (3 H, m, 3 CH), 7.75-8.05 (2 H, br. s, NH_2), 7.89 (2 H, d, J = 7.6 Hz, 2 CH), 8.40 (2 H, d, J = 7.9 Hz, 2 CH). ^{13}C NMR (75.5 MHz, DMSO - d_6): δ 21.05 (CH_3), 84.06 (CN), 116.60 (C), 128.44, 128.51, 128.61 and 129.08 (4 CH), 131.53, 133.78, 136.65 and 141.02 (4 C), 163.96, 164.72 and 167.92 (3 C-N).

4-amino-2-(4-methylphenyl)-6-phenyl-5-pyrimidinecarbonitrile (5e)

Colorless crystals. ^{1}H NMR (300.1 MHz, DMSO - d_6): δ 2.36 and 2.39 (6 H, 2 s, 2 CH_3), 7.30 (2 H, d, J = 8.1 Hz, 2 CH), 7.36 (2H, d, J = 8.1 Hz 2 CH), 7.65 – 7.95 (2 H, br. s, NH_2), 7.88 (2 H, d, J = 8.1 Hz, 2 CH), 8.30 (2H, d, J = 8.2Hz, 2 CH). ^{13}C NMR (75.5 MHz, DMSO - d_6): δ 2.12 (CH_3), 55.42 (OCH_3), 83.10 (CN), 113.87 (CH), 116.91 (C), 128.44 (CH), 128.80 (C), 129.09 and 130.39 (2 CH), 134.03 and 141.45 (2 C), 161.54 (C-O), 163.86, 164.78, and 167.11 (3 C–N).

4-amino-6-(4-methoxyphenyI)-2-phenyl-5-pyrimidinecarbonitrile (5f)

Colorless crystals. ^{1}H NMR (300.1 MHz, DMSO - d_6) δ 3.94 (3 H, s, OCH_3), 7.12 (2 H, d, J = 8.9 Hz, 2 CH), 7.46-7.55 (3H, m, 3CH), 7.65 - 8.05 (2 H, br. s, NH_2), 8.02(2 H, d, J = 8.8 Hz, 2CH), 8.40 (2H, d, J = 7.9 Hz, 2 CH). ^{13}C NMR (75.5 MHz, DMSO - d_6): δ 55.45 (OCH_3), 83.40 (CN), 113.93 (CH), 116.85 (C), 128.42, 128.51, 128.74, and 130.44 (4 CH), 131.49 and 136.70 (2 C), 161.59 (C–O), 163.84, 164.83, and 167.21 (3 C-N)

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