Reactions of Ketene: Synthesis of Polysubstituted Pyrimidine derivatives

Article · February 2019

CITATIONS
0

READS
10

7 authors, including:

Babasaheb Aware
Alkem Laboratories Ltd.
10 PUBLICATIONS **180** CITATIONS
SEE PROFILE

Raghunath B Toche
KRT Arts, BH Commerce and AM Science (KTHM) College, Nashik
100 PUBLICATIONS **698** CITATIONS
SEE PROFILE

Satish Chavan
R.N.C. Arts, J.D.B. Commerce & N.S.C. Science College, Nashik-Road, Nashik
14 PUBLICATIONS **12** CITATIONS
SEE PROFILE

Poonam shyam Patil
KRT Arts, BH Commerce and AM Science (KTHM) College, Nashik
5 PUBLICATIONS **5** CITATIONS
SEE PROFILE

RESEARCH JOURNEY International Multidisciplinary E-Research Journal | ISSN- 2348-7143
Impact Factor - (SJIF) – 6.261, (CIF) - 3.452, (GIF) –0.676 Special Issue - 118 | February 2019 | UGC Approved No. 40705
Modern Trends in Green Chemistry, Medicinal Chemistry and environmental Science

Reactions of Ketene: Synthesis of Polysubstituted Pyrimidine derivatives

Pankaj B. Aware*[1], Raghunath B.Toche[2], Ashok P.Pingle[3], Satish M.Chavan[4], Poonam S.Patil[1], Sandeep D.Pardeshi[5], Jayant P. Sonar[5]

[1] Dept. of Chemistry KRT Arts, BH Commerce and AM Science College, Nashik -02, Maharashtra,
[2]Dadasaheb Bidkar Arts, Commerce and Science College Peth, Nashik, Maharashtra, India
[3] MVP Samaj's College of Pharmacy Nashik-02, Maharashtra, India
[4] Department of Chemistry, RNC Arts, JDB Commerce and NSC Science college, Nashik
[5]Department of Chemistry, Vinayakrao Patil Mahavidyalaya, Vaijapur. Aurangabad, Maharashtra, India

---

ABSTRACT

4-substituted-5-carbonitriles were synthesized by condensation reaction of ketene with substituted urea in presence of anhydrous K_2CO_3 in *N*,*N*-dimethylformamide. Further 4-methylthio group was substitutes by morpholine to obtain 4-morphalino pyrimidine derivatives. The new compounds were characterized by analytical spectroscopic studies

Introduction:

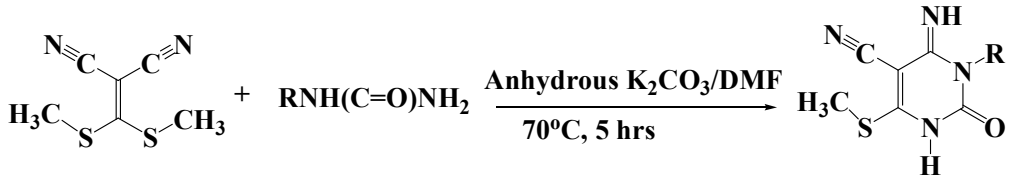
Pyrimidine represents a broad class of compounds,which have received considerable attention due to their wide range of biological activities such as ,anti –inflammatory, COX inhibitor, anticancer, antiallergic analgesic [1-2]. Inflammation is a normal bodily protective response to tissue injury caused by physical trauma, noxious chemical or microbial infection and characterized by hears, redness, pain, swelling and disturbed physiological functions [3-4)]. It is a complex process, which is frequently associated with increase in vascular permeability, increase of protein denaturation and membrane alternations [5].

On the basis of literature review it has been found that the substituted pyrimidine derivatives have good potential to exhibit *in vitro* anti –inflammatory activity [6-7].In present work substituted pyrimidine derivatives were synthesized. Compounds which are devoid of any of these toxic ettects and at the same time, also exhibiting the predicted anti–inflammatory activity Pa <0.5>0.3 were selected independently for *in vitro* anti–inflammatory activity screening (8).

We have reported the synthesis of these compounds by conventional method. The product obtained by this method was identical, confirmed by scanning the IR, NMR, MP, mixed MP and TLC method.

Results and Discussion

1. Synthesis of 1,2,3,6–tetrahydro-6–imino–4-(methylthio)–2-oxo-1-substitutedpyrimidine-5-carbonitrile 3(a-c).



1 **2** **3(a-c)**

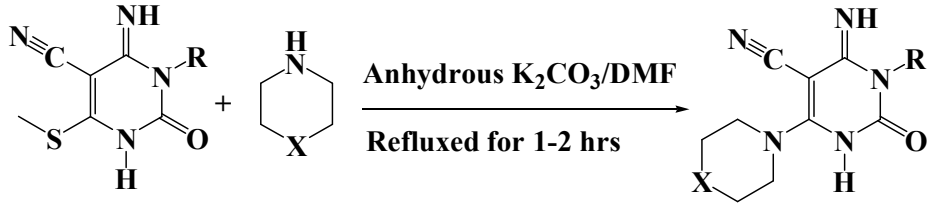
Scheme 1

3a,R=Ph ;3b,R=CH_2 Ph;3c,R=CH_3

1,2,3,6-tetrahydro-6-imino-4-(methylthio)-2-oxo-1-phenylpyrimidine-5-carbonitriles **3** were obtained by condensation of 2-(bis(methylthio)methylene)malononitrile**(1)** with substituted urea (2a-c)and anhydrous K_2CO_3 and DMF**(3),** at 70°C, in 75% yield.

The ^{1}HNMR of **3a** showed that aromatic protons at δ=7.11-8.48 as multiplates,and singlet at δ 2.9 was correspond to NH group. The compound was analysed for molecular formula $C_{12}H_{10}N_4OS$. Based on the spectral and anaytical data, structure **3a** was assigned to this experimental product.The spectral and physical data of all compounds are explained in experimental part .

2 Synthesis of 1,2,3,6 – tetrahydro – 6 – imino – 4 – morpholino – 2 – oxo – 1- substitutedpyrimidine-5-carbonitrile(5a-c).



3(a-c) **Scheme II** **5(a-c)**

X = O,CH_2 5a,R=Ph ;5b,R=CH_2 Ph;5c,R=CH_3

As envisioned in our scheme the compound **3** was reacted with secondary amine **4** in presence anhydrous K_2CO_3 and DMF at refluxed temp for 1-2hr (TLC check by hexane: ethyl acetate) then the reaction mixture was poured in ice cold water. The solid separated was filtered, dried and crystallized from suitable solvent.
The IR of the compound **5a** showed the presence of C=O frequency at 1660 cm^{-1} and the singles at 2250 cm^{-1} including the presence of nitrile functionality and including the presence of other functionality.
The ^{1}HNMR ($CDCl_3$) of **5a** showed the presence of the compound was analysed for molecular formula $C_{15}H_{15}N_5O_2$.The spectral and physical data of all compounds are explained in experimental part.

Experimental

1) Synthesis of 1,2,3,6-tetrahydro – 6 – imino – 4-(methylthio) – 2-oxo-1-substituted pyrimidine-5-carbonitrile (3a-c).

The mixture of 2-(bis(methylthio)methylene)malononitrile(2.17g;0.01 mole) and substituted urea (1.2g; 0.01 mole) were refluxed in the presence of 20-25 ml of DMF and a pinch of anhydrous K_2CO_3 for 5 h .The reaction mixture was cooled to room temperature and poured in ice-cold water. The separated solid product was filtered, washed with water, dried and recrystallized from ethanol to give pure crystalline solid product.

1,2,3,6-Tetrahydro-6-imino-4-(methylthio)-2-oxo-1-phenylpyrimidine-5-carbonitrile 3a :

1) Yield 60%, m.p.- 300°C(decompose); IR(KBr): cm^{-1}=3412, 3350,2250, 1630, 1540, 1400.; ^{1}HNMR: δ=7.00-7.64(m; 5H, Ar-H), 2.25(s; 3H, CH_3), 6.0(s; 1H, NH), (s;1H,=NH) ppm;

2) 1–Benzyl-1,2,3,6-tetrahydro-6-imino-4-(methylthio)-2-oxopyrimidine-5-carbonitrile 3b :-

Yield 55%, m.p.- 300°C(decompose); IR(KBr): cm^{-1}=3412, 3350, 2250, 1630, 1540, 1424.^{1}HNMR: δ=7.06-7.17(m; 5H, Ar-H), 2.25(s; 3H, CH_3), 4.42 (s; 2H ,CH_2) 6.0(s; 1H, NH)), (s;1H,=NH) ppm;

3) 1,2,3,6-Tetrahydro-6-imino1methyl-4-(methylthio)-2-oxopyrimidine-5-carbonitrile 3c :

Yield 60%, m.p.-300°C(decompose); IR(KBr): cm^{-1}=3400, 3340,2245, 1650, 1535, ^{1}HNMR:δ=2.25(s;3H,CH_3), 2.74(s;3H,CH_3) 6.0(s; 1H, NH),(s;1H,=NH) ppm;

2) Synthesis of 1,2,3,6-tetrahydro-6-imino-4-morpholino-2-oxo-1-substituted pyrimidine-5-carbonitrile 5(a-c).

The mixture of 1,2,3,6-tetrahydro-6-imino-4-(methylthio)-2-oxo-1-substituted pyrimidine-5-carbonitrile **3**(0.01mol), secondary amines **4** (0.01mol) was refluxed in the presence of 20-25 ml of DMF with a pinch of anhydrous K_2CO_3.The reaction mixture was cooled to room temperature and poured in ice-cold water. The separated solid product was filtered, washed with water, dried and recrystallized from ethanol to give pure crystalline solid product.

1)1,2,3,6-Tetrahydro-6-imino-4-morpholino-2-oxo-1-phenylpyrimidine-5-carbonitrile 5a :

Yield 60%, M.P.-300°C(decompose); IR(KBr): cm-1 3209, 2925,2206, 1656,1508, 1469,1333.; ^{1}HNMR: δ 7.00-7.64(m; 5H, Ar-H), 2.25(s; 3H, CH_3), 6.0(s;1H, NH) ppm

2)1-benzyl-1,2,3,6-tetrahydro-6-imino-4-morpholino-2-oxo-1-phenylpyrimidine-5-carbonitrile 5b:

Yield 55%, M.P.-300°C(decompose); IR(KBr): cm-1 3220, 3050, 2250, 1630,1540, 1424 . ^{1}HNMR: δ 7.06-7.17(m; 5H, Ar-H), 2.25(s; 3H, CH3), 4.42 (s; 2H,CH_2) 6.0(s; 1H, NH)), (s;1H, NH) ppm;

3)**1,2,3,6-Tetrahydro-6-imino-1methyl-4-morpholino-2-oxo-1-phenylpyrimidine-5-carbonitrile 5c:**

Yield 60%, M.P.-300°C(decompose); IR(KBr): cm-3209, 2925, 1650, 1535,^{1}HNMR:δ2.74(s;3H,CH_3)2.9 (d; 4H ,CH_2) ,3.67 (d; 4H ,CH_2) ,6.0(s; 1H, NH)ppm

Acknowledgements

Pankaj B Aware thanks to CIF, SPPU, Pune for spectral analysis; Sarchitnis, Maratha Vidhya Prasarak Samaj, Nashik 422 002; Principal, KRT Arts, BH Commerce and AM Science College, Nashik 422 002 (MS), India for facilities

References

[1] Zienab MN, Hoda HF, Eman SZ, Wafaa EE. *Acta Poloniae Pharmaceutica Drug Research*. 2011;68:507-517.
[2] Sham MS, Nirupma S, Monika J, Ashok K. *Bioorganic & Medicinal Chemistry*. 2005;13:6158-6166.
[3] Sangita C, Priyanka C, Protapaditya D, SanjibB. *Asian Pacific Journal of Tropical Biomedicine*; 2012:170-180.
[4] Sangita C, Priyanka C, Protapaditya D, Sanjib *B Journal of Advanced Pharmacy Education & Research*. 2012;2:25-31.
[5] Padmanabhan P, Jangle SN. *International Journal of Basic and Applied Medical Sciences*. 2012;2:109-116.
[6] Alexy L, Alla S, Dmitrii F. *PASS: Bioinformatics Application Note*.2000; 16:742-748.
[7] PramelyJuss R, Leon S.R *T. J Biochem Tech*. 2012:3.
[8] RajaSekhar KK, Rajendra Prasad Y. *Journal of Global Trends in Pharmaceutical Sciences.* 2011;2:489-512.
[9] Sushilkumar SB, Devanand BS .*Bioorganic & Medicinal Chemistry Letters.* 2004;14:1733-1736.
[10] Tomasz P, Marcin S, Elz_bieta *W*. 1-12.
[11] Takjoo Reza. *Molecules.*2009;14:4849-4857.
[12] Yang HZ, Liu HY, Yang GF. *Chinese Chemical Letters*. 1999;10:191-192.
[13] Vartale SP, Kalyankar ND, Halikar NK. *Journal of Chemical and Pharmaceutical Research*. 2012;4:186-191.
[14] Vartale SP, Halikar NK, Pawar YD. *Journalof Chemistry*. 2013:1-7.
[15] Balakumar C, Kishor DP, VenkatRao K, etal.*Indian Journal of Chemistry*.2012;51B:1105-1113.
[16] Mizushima Y, Kobayashi M. *Journal of Pharma Pharmacology*.1968;20:169-173.
[17] Mizushima Y, Kobayashi M. *Journal of Pharma Pharmacology*.1968;20:169-173.
[18] Satish M. Chavana, Raghunath B. Toche, Vasant M. Patil, Pankaj B. Aware and Poonam S. Patil