



A Simple and Efficient Synthesis of 2, 4 dioxypyrimidine carboxylate and 4-oxo-2-thioxypyrimidine carboxylate derivatives using Ammonium Chloride

Aher J. S.^a, Gaware M. R.^{b,*}, Lokhande D. D.^a, and Tambade P. J.^b

^a Department Chemistry, MVP Samaj's KTHM College, Nashik (MS) India.

^b Department of Chemistry, MVP Samaj's Arts, Commerce & Science College, Nandgaon Nashik. (MS) India

[*Corresponding Author's E-mail: gawaremanoj@rediff.com]

Abstract: An efficient and simple protocol has been developed for the synthesis of 4-oxo-2-thioxypyrimidine carboxylate and 2,4 dioxypyrimidine carboxylate derivatives using ammonium chloride as a catalyst. Various substituted 4-oxo-2-thioxypyrimidine carboxylate and 2, 4 dioxypyrimidine carboxylate derivatives was synthesized by ternary condensation of diethyl malonate, aromatic aldehyde and thiourea/urea by using ammonium chloride. Structures of all the products are supported by their spectral data.

Keywords: Biginelli reaction, ammonium chloride, diethyl malonate, aldehydes

1 Introduction

Synthesis of heterocyclic compounds containing O, S, and N along with broad spectrum of biological activity (1-13) such as antiviral, antibacterial, anticancer, antifungal, antioxidant, antimalarial, anti HIV, sedatives, anticonvulsant, antihistamic agent, antihypertensive, anti-inflammatory, and calcium channel blockers of oxo and thioxo pyrimidine carboxylate derivatives, has been reported in this paper. Pyrimidines and fused pyrimidines is an essential part of DNA and RNA, plays an vital role in several biological processes. The thiouracil derivatives can be utilized as a component and adhesive for noble metals in many fields such as medical treatment, electronic materials, precision instruments and jewelry where resins

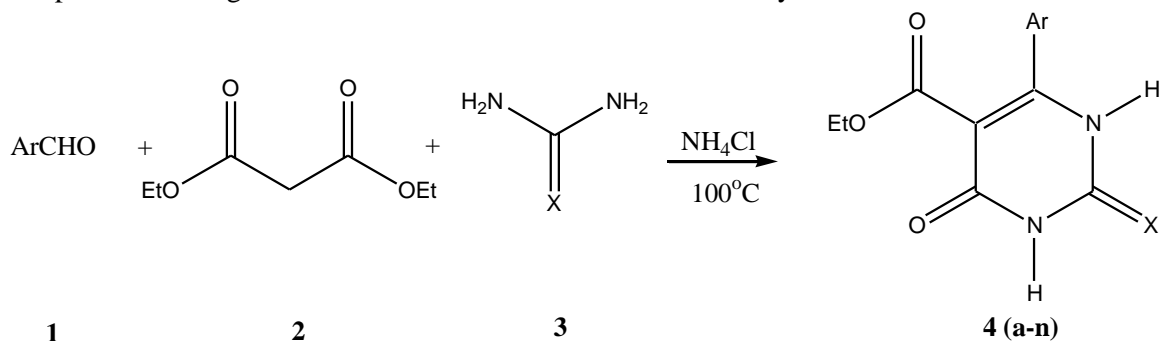
are bonded to metals and are particularly useful in the dental field (14). On account of these reasons synthesis of heterocyclic compounds is of great interest.

2 Results and Discussion

The reaction of substituted aromatic aldehydes, diethyl malonate and urea/thiourea in presence of ammonium chloride for 3 hrs gives product (a-n) with high yields. Very few literature has been reported regarding synthesis of oxo and thioxo pyrimidine carboxylate derivatives. One of the method involves synthesis of 4-oxo-6-substituted phenyl-2-thioxo-1,2,3,4 tetrahydropyrimidine-5-carbonitrile (15-22) followed by hydrolysis and esterification using ethanol to give desired product. But this method is time consuming and

produces product with low yield. Apart from this there is no report on this synthetic route according to our knowledge. Therefore, we have developed a new protocol by using inexpensive reagent in solvent free

condition at 100 °C. Under optimized conditions various derivatives were synthesized and selected products were characterized by physical constant, IR and NMR analysis.



Ar = -C₆H₅, 4-(Cl)-C₆H₄, 4-(OH)-C₆H₄, 2-furyl
X = O,S

Scheme 1: Synthesis of heterocyclic compounds using NH₄Cl as a catalyst

Table 1 : Synthesis of 2,4 dioxypyrimidine carboxylate and 4-oxo-2-thioxopyrimidine carboxylate under solvent free condition using ammonium chloride

Compound	Ar	X	Yield (%)	m.p. (°C)
4a	-C ₆ H ₅	O	72	210-212
4b	4-(Cl)-C ₆ H ₄	S	84	214-216
4c	4-(OH)-C ₆ H ₄	S	82	218-220
4d	C ₆ H ₅	S	70	238-240
4e	2-furyl	O	76	196-198
4f	4-(Cl)-C ₆ H ₄	O	80	240-242
4g	3-(Cl)-C ₆ H ₄	S	83	194-196
4h	4-(OH)-C ₆ H ₄	O	87	224-226
4i	2-furyl	S	81	208-210
4j	3-(Cl)-C ₆ H ₄	O	65	206-208
4k	3-(NO ₂)-C ₆ H ₄	O	72	224-228
4l	4-(OCH ₃)-C ₆ H ₄	S	88	230-232
4m	3-(NO ₂)-C ₆ H ₄	S	70	218-220
4n	4-(OCH ₃)-C ₆ H ₄	O	74	225-227

Reaction conditions: Aldehyde (2 mmol), ethyl acetoacetate (2 mmole), thiourea (3 mmole) and NH₄Cl (0.8 mmol), temperature (100 °C), time: 3h.

In order to get product in good yield various reaction parameters were optimized, we checked effect of temperature, stoichiometry of reactants, time on yield of product. The

reaction was carried out using various stoichiometric ratios of reactants. The excellent results were obtained with 0.5:1:1:1.5 ratio of ammonium chloride,

Page 44

aldehyde, ethyl acetoacetate and urea/thiourea (Table 1). From table 1, aldehyde, diethyl malonate, urea/thiourea, in presence of NH₄Cl affords corresponding 2,4 dioxypyrimidine carboxylate and 4-oxo-2-thioxopyrimidine carboxylate under neutral condition in good to excellent yields in 3 hours. The optimized reactions conditions were then used for preparation of derivatives. We have checked effect of electron donating and withdrawing groups on yield of product. From table 1 it is depicted that electron donating group like -CH₃, -OCH₃, -OH furnishes product with good yield, however, electron withdrawing functionality like -NO₂ provides product in moderate amount.

3 Experimental Section

All the reagents used are of research grade purchased from S. D. Fine, Merck. Melting points were recorded on open capillary method and are uncorrected. The melting points were compared with literature. Synthesized products were characterized by IR and ¹H NMR. Infrared (IR) spectra were recorded on Shimadzu FTIR spectrometer. ¹H NMR Spectra were recorded on Bruker Advance II (400 MHz) using DMSO-d₆ as a solvent.

General Procedure for Synthesis of 2,4 dioxypyrimidine carboxylate and 4-oxo-2-thioxopyrimidine carboxylate:

A mixture of benzaldehyde (0.30 g, 2 mmol), diethyl malonate (0.26 g, 2 mmole), thiourea (0.18 g, 3 mmole) and NH₄Cl (0.05 g, 0.8 mmol) was heated under stirring at 100 °C for 3 hrs. After cooling, solid product obtained was filtered and washed with cold water. It was further recrystallized from ethanol or ethyl acetate: *n*-hexane (1:3) to have analytical sample for spectral analysis.

Spectral data of synthesized compounds:

Compound 4l:

ethyl 1,2,3,4- tetrahydro-6- (4-methoxyphenyl) -4-oxo-2-thioxopyrimidine-5-carboxylate:

m.p. 230-232 °C, IR: 3375, 3271, 3167, 2689, 1762, 1609, 1465, 1404, 1246, 1083, cm⁻¹. ¹H NMR (DMSO-d₆ 400 MHz) 9.86 δ

(s, -NH), 7.84 δ (d, 1 H, ArH), 7.86 δ (d, 1 H, ArH), 7.43 δ (d, 1 H, ArH), 7.45 δ (d, 1 H, ArH), 3.4 δ (s, -OCH₃), 3.89 δ (q, OCH₂), 1.20 δ (t, -CH₃)

Compound 4d:

ethyl 1,2,3,4-tetrahydro-4-oxo-6-phenyl-2-thioxopyrimidine-5 carboxylate:

m.p. 238-240 °C, IR: 3371, 3263, 3055, 2341, 1748, 1612, 1435, 1400, 1361, 1184, 1114 cm⁻¹. ¹H NMR (DMSO-d₆ 400 MHz): 8.2δ (s, -NH), 7.04-7.37δ (m, 5 H, ArH), 3.50 δ (q, OCH₂), 1.10 δ (t, -CH₃)

Compound 4f:

ethyl 6-(4-chlorophenyl)-1,2,3,4-tetrahydro-2,4-dioxypyrimidine-5-carboxylate:

m.p. 240-242 °C, IR: 3367, 3163, 2337, 1760, 1605, 1465, 1408, 1183 cm⁻¹. ¹H NMR (DMSO-d₆ 400 MHz) : 8.15 δ (s, -NH), 7.42 δ (d, 1 H, ArH), 7.40 δ (d, 1 H, ArH), 7.38 δ (d, 1 H, ArH) 7.36 δ (d, 1 H, ArH), 3.61 δ (q, OCH₂), 1.16 δ (t, -CH₃)

4 Conclusion:

In conclusion, we have developed an economical and environment friendly protocol for the synthesis of 2,4 dioxypyrimidine carboxylate and 4-oxo-2-thioxopyrimidine carboxylate with short reaction time, inexpensive and easily available catalyst and solvent free condition. The readily available ammonium chloride is explored as catalyst for this reaction which affords clean and excellent yields of product. Effect of electron donating and withdrawing functionality on product yield was checked.

5 Acknowledgment:

The authors thanks, Principal, Arts, Commerce and Science College, Nandgaon, M.V.P Samaj, Nashik for infrastructural support. We are also thankful to Principal, K.T.H.M College for providing research laboratory facilities and spectral analysis data.

6 References

1. Kappe C. O., *Tetrahedron* (1993), 49, 6937.

2. (a) Patil A. D., Kumar N. V., Kokke W. C., Bean M. F., Freyer A. J., De Brosse., Mai C., Trunch A., Faulkner D. J., Carte B., Breen A. L., Hertzberg R. P., Johnson R. K., Westley J., Wand Potts B. C., *J. Org. Chem.* (1995), 60, 1182. (b) Snider B. B., Chen J., Patil A., DandFreyer A., *Tetrahedron Lett.* (1996), 37, 6977.
3. Clark J., Shahhet M. S., Korakas D., and Varvounis G., *J.Het.Chem.* (1993), 30 1065.
4. Ogowva K., Yamawaki I., Matsusita Y. I., Nomura N., Kador P. F., Kinoshita J. H., *Eur. J. Med.Chem.* (1993), 28, 769.
5. Tozkoparan B., Ertan M., Kelicen P., Demirdar R., *Farmaco* (1999), 54, 588.
6. Santagati M., Modica M., Santagati A., Russo F., Spampinato S., *Pharmazie* (1996), 517.
7. Ahluwalia V. K., Chopra M., Chandra R. A., *J. Chem. Res.* (2000), 162.
8. Van Laar M., Volkerts E., Verbaten M., *Psychopharmacology* (2001), 154, 189.
9. Danel K., Pedersen E., Band Nielsen C., *J. Med. Chem.* (1998) 41, 191.
10. Fathalla O. A., Awad S. M., Mohamed M. S., *Arch. Pharm. Res.* (2005), 28, 1205.
11. Fathalla O. A., Zaghary A., Radwan H. H., Awad S. M., Mohamed M. S., *Arch. Phar. Res* (2002), 25, 258.
12. Ding Y., Girardet J., Smith K. L., Prigaro G. L., Wu J. Z. Yao N., *Bioorg. Chem.* (2006), 34, 26.
13. Azza T., Sahar M. A., *Molecules* (2012), 17, 9868.
14. Kimura M., Aizawa M., *USP 15005795497161A5* (1998), 795, 497.
15. Kambe S., Saito K., Kishi H., *Synthesis* (1979), 287.
16. Patel A., Pasha T. Y., Modi A., *Int. J. Phar. Tec. Res.* (2015), 8, 136.
17. Murthy Y. L. N., Saveri R. M. R., Parimi A. R., *S.Org. Com.* (2013), 6, 1, 47.
18. Eweas A F., Qasem M. A., Abdallah Emad S. I. Hassan., *J. App. Phar. Sci* (2014), 4, 12, 102.
19. Mohamed M. S., Awadn S. M., Ahmed A. M., *Act. Phar.* (2011), 61, 171.
20. Chitre T. S., Bothara K. G., *Der. Chem. Sin.* (2011), 2, 2, 187.
21. Muftah M. S., Abuhamrah S. E., *Int. J. Adv. Res. Bio. Sci.* (2014), 1, 9, 259.
22. Desai S. A., Bhatia M. S., Choudhari P. B., Ingale K. B., *Int. J. Pharm. Sci. Res.* (2014), 5, 6, 241.