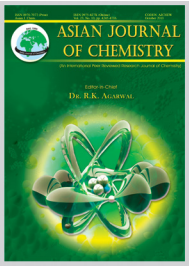
Asian Journal of Chemistry; Vol. 24, No. 3 (2012), 1293-1296

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Synthesis of New Asymmetrical Dihydropyrimidinones in Presence of Oxalic Acid

BEHROOZ MIRZA[1,*] and SEPEHR SADEGH SAMIEI[2]

[1]Department of Chemistry, Faculty of Sciences, South Tehran Branch, Islamic Azad University, Tehran, Iran
[2]Department of Chemistry, Faculty of Sciences, East Tehran Branch (Qiam Dasht), Islamic Azad University, PO Box 33955-163, Tehran, Iran

*Corresponding author: E-mail: b_mirza@azad.ac.ir

(*Received*: 6 April 2011; *Accepted*: 12 November 2011) AJC-10643

An efficient synthesis of asymmetrical branched dihydropyrimidinone derivatives using oxalic acid as a catalyst for the first time from multicomponent reaction of aromatic dialdehydes, β-diketones, urea and thiourea in refluxing acetonitrile is described.

Key Words: Dihydropyrimidinone, Biginelli reaction, Multicomponent reactions, Oxalic acid, Asymmetrical synthesis.

INTRODUCTION

Dihydropyrimidinones (DHPMs) and their derivatives exhibit extensive activities such as antibacterial, antiviral, anti-infamatory, antitumor and also show a very similar pharmacological profile to classical dihydropyrimidine calcium channel modulators[1-8]. Moreover these compounds demonstrate the other pharmacological activities as antihypertensive agents, α-1a-antagonists and neuropeptide Y(NPY) antagonists[9]. Batzlladin B, an alkaloid containing the dihydropyridimidine-5-carboxylate unit, that has been isolated from marine sources, was found to be potent HIV-gp-120-CD4 inhibitor[10]. Therefore, the synthesis of this heterocyclic core unit is of much current importance.

Both economic and ecological pressures, coupled with the concomitant emergence of high throughput screening, are playing increasing significant roles in the development of modern synthetic organic chemistry[11] selectivity, atom economy[12-14] time saving, environmental friendliness, cost effectiveness and the reconciliation of molecular complexity with experimental simplicity are some of the pieces of the puzzle needing to be assembled by modern academic and industrial synthetic chemists to reach the maximum of efficiency[15]. To achieve these goals, utilization of multicomponent reactions (MCRs) with at least three different simple substrates[16,17] reacting in a well defined manner to form a single compound, has emerged as a powerful strategy[18]. Biginelli was a pioneer in this field and reported his first empirical observation of multi component reaction (MCR) in 1893.

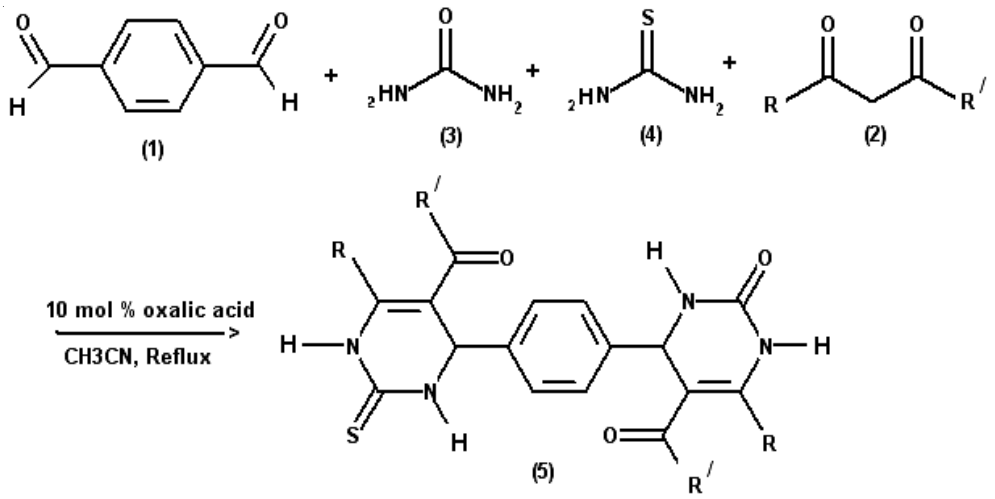
Beginilli synthesized dihydropyrimidinones through one-pot three component condensation of β-ketoesters, aldehydes and urea in refluxing ethanol containing a catalyst amount of HCl[19]. In spite of its high simplicity, this method suffers from long reaction times and low to moderate yields (20-60 %) especially with aliphatic and some substituted aromatic aldehydes. Some other protic acid promoters, such as *p*-toluenesulfonic acid (PTSA)[20], potassium hydrogen sulfate[21], or reusable silica sulfuric acid[22], have been used in order to overcome these disadvantages.

Despite all efforts to improve the yield of Beginelli reaction, there was always the lacuna in diversity enhancement of synthesized molecules. We recently reported[23] the synthesis of symmetrical dihydropyrimidin-2 (1*H*)-one through the reaction of terephthalic aldehyde, urea and β-diketone derivatives in MeCN in the presence of TMSCl at room temperature. But in view of the current thrust in enhancement of molecular diversity, we report in this communication for the first time the asymmetric synthesis of dihydropyrimidinones catalyzed by oxalic acid (**Scheme-I**).

EXPERIMENTAL

Melting points were determined in a capillary tube and uncorrected. The ^{1}H NMR spectra were recorded on a FT-NMR Bruker Spectro Spin DRX-300 MHz instrument as DMSO-d_6 solutions and the chemical shifts are expressed as d units with Me_4Si as the internal standard. Mass spectra were obtained on a MS Model 5973 Network apparatus at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. FT-IR spectra were recorded using KBr disks on a Bomem-MB 100 infrared spectrometer and absorptions are reported as wave numbers (cm^{-1}).

Typical procedure: A solution of terephthalic aldehyde (1 mmol), urea (1.5 mmol), thiourea (1.5 mmol), 1,3- dicarbonyl



Scheme-I: Reaction of terephthalic aldehyde, urea, tiourea and b-diketones

compound (2 mmol) and catalytic amount of oxalic acid (10 mol %) in acetonitrile (5 mL) was heated at the temperature of 80 °C. The mixture was kept stirring for 1 h. Then it was cooled down to room temperature. The mixture was then poured into 20 mL of ice-water and was kept stirring for about 10 min. The solid products were filtered and washed with ice-water (2 × 10 mL) and then ethanol 90 % (10 mL) to give the pure product.

5a: Yield 83 %, m.p. > 300 ºC, IR (KBr, ν_{max}, cm^{-1}) 3322, 3251, 2945, 1690, 1680, 1660, 1457, 1226 (C=S); ^{1}H NMR (DMSO-d_6) δ 10.26 (sbr, 1H, NH), 9.71 (sbr, 1H, NH), 9.16 (sbr, 1H, NH),7.77 (sbr, 1H, NH), 7.18-7.25 (m, 4H, Ar), 5.21 (s, 1H, CH), 5.11 (s, 1H, CH), 2.31 (s, 3H, COMe), 2.27 (s, 3H, COMe), 2.16 (s, 3H, Me), 2.10(s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ 193.5, 190.2 175.6, 165.5, 143.7,141.3, 133.2, 130.9, 125.4, 122.2, 114.4, 110.8, 59.1, 54.2, 30.5, 29.9, 15.9, 15.1; MS (70 eV) m/z (%) 398 (M^+, 10), 383 (15), 368 (21), 282 (83), 152 (87), 77 (67), 59 (89), 43 (100).

5b: Yield 87 %, m.p. >300 ºC, IR (KBr, ν_{max}, cm^{-1}) 3353, 3239, 3117, 2928, 1715, 1705, 1650, 1223 (C=S); ^{1}H NMR (DMSO-d_6) δ 10.43 (sbr, 1H, NH), 10.31 (sbr, 1H, NH), 9.72 (sbr, 1H, NH), 9.61 (sbr, 1H, NH), 7.20-7.28 (m, 4H, Ar), 5.25 (d, J = 3Hz, 1H, CH), 5.13 (d, J = 3 Hz, 1H, CH), 4.01 (q, J = 7Hz, 2H, OCH_2CH_3), 3.87 (q, J = 7Hz, 2H, OCH_2CH_3), 2.30(s, 3H, Me), 2.27(s, 3H, Me), 1.10 (t, J = 7Hz, 3H, OCH_2CH_3), 1.04 (t, J = 7Hz, 3H, OCH_2CH_3); ^{13}C NMR (DMSO-d_6): δ 192.5, 189.1, 175.8, 165.3, 146.5, 143.8, 136.5, 133.8, 128.1, 127.5, 101.5, 100.8, 58.3, 56.2, 54.6, 52.4, 32.3, 30.4, 18.1, 17.9. MS (70 eV) m/z (%) 458 (M^+, 6), 428 (7), 368 (10), 284 (100), 268 (71), 60(83).

5c: Yield 88 %, m.p. > 300 ºC, IR (KBr, ν_{max}, cm^{-1}) 3324, 3248, 2961, 2930, 1710, 1673, 1236 (C=S); ^{1}H NMR (DMSO-d_6) δ 10.36 (sbr, 1H, NH), 9.65 (sbr, 1H, NH), 9.23(sbr, 1H, NH), 7.78 (sbr, 1H, NH), 7.49-7.39 (m, 10H, COPh), 7.15-7.20 (m, 4H, Ar), 5.24 (d, J = 3Hz, 1H, CH), 5.20 (d, J = 3 Hz, 1H, CH), 1.93 (s, 3H, Me), 1.87 (s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ 195.1, 194.6, 175.4, 153.1, 152.9, 151.5, 148.6, 146.6, 145.7, 144.1, 141.8, 140.2, 130.7, 129.5, 128.6, 127.8, 127.2, 126.1, 112.3, 110.2, 33.7, 31.9; MS (70 eV) m/z (%) 422 (M^+, 6), 507 (9), 492 (11), 415 (18), 310 (23), 282 (100), 152 (81), 120 (54), 106 (67), 77 (82).

5d: Yield 83 %, m.p. >300 ºC, IR (KBr, ν_{max}, cm^{-1}) 3320, 3233, 2973, 2955, 1708, 1683, 1241 (C=S); ^{1}H NMR (DMSO-d_6) δ 10.25 (sbr, 1H, NH), 9.74 (sbr, 1H, NH), 9.27 (sbr, 1H, NH), 7.81 (sbr, 1H, NH), 7.45-7.85 (m, 8H, COPh), 7.12-7.17 (m, 4H, Ar), 5.21 (d, J = 3Hz, 1H, CH), 5.17 (d, J = 3Hz, 1H, CH), 1.71(s, 3H, Me), 1.65 (s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ 195.1, 194.6, 175.4, 153.1, 152.9, 151.5, 150.2, 149.1, 148.6, 147.2, 146.6, 145.7, 144.1, 142.8 130.7, 129.5, 128.6, 127.8, 127.2, 126.1, 33.8, 31.9; MS (70 eV) m/z (%) 594 (M + 4$^+$, 2), 592 (M + 2$^+$, 12), 590 (M^+, 18), 479 (100), 415 (18), 310 (23), 152 (81), 112 (54), 106 (67), 77 (82).

5e: Yield 81 %, m.p. >300 ºC, IR (KBr, ν_{max}, cm^{-1}) 3343, 3222, 2967, 2947, 1711, 1675, 1243 (C=S); ^{1}H NMR (DMSO-d_6) δ 10.31 (sbr, 1H, NH), 9.82 (sbr, 1H, NH), 9.31 (sbr, 1H, NH), 7.87 (sbr, 1H, NH), 7.32-7.57 (m, 8H, COPh), 7.14-7.21 (m, 4H, Ar), 5.10 (d, J = 3Hz, 1H, CH), 5.04 (d, J = 3Hz, 1H, CH), 1.68 (s, 3H, Me), 1.62 (s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ 195.4, 194.9, 175.7, 153.8, 153.1, 152.9, 151.2, 149.7, 148.8, 147.6, 146.9, 146.1, 144.8, 143.1 130.4, 129.1, 128.3, 127.2, 127.0, 126.5, 32.1, 31.4; MS (70 eV) m/z (%) 522 (M^+, 6), 507 (9), 492 (11), 415 (18), 310 (23), 282 (100), 152 (81), 120 (54), 106 (67), 77 (82).

5d: Yield 83 %, m.p. >300 ºC, IR (KBr, ν_{max}, cm^{-1}) 3320, 3233, 2973, 2955, 1708, 1683, 1241 (C=S); ^{1}H NMR (DMSO-d_6) 10.25 (sbr, 1H, NH), 9.74 (sbr, 1H, NH), 9.27 (sbr, 1H, NH), 7.81 (sbr, 1H, NH), 7.45-7.85 (m, 8H, COPh), 7.12-7.17 (m, 4H, Ar), 5.21 (d, J = 3Hz, 1H, CH), 5.17 (d, J = 3Hz, 1H, CH), 1.71(s, 3H, Me), 1.65 (s, 3H, Me); ^{13}C NMR (DMSO-d_6): δ 195.1, 194.6, 175.4, 153.1, 152.9, 151.5, 150.2, 149.1, 148.6, 146.6, 145.7, 144.1, 130.7, 129.5, 128.6, 127.8, 127.2, 126.1, 33.8, 31.9; MS (70 eV) m/z (%) 682 (M + 4$^+$, 6), 680 (M + 2$^+$, 12), 658 (M^+, 6), 525 (100), 368 (23), 282 (12), 185 (81), 157 (54), 106 (67), 77(82).

RESULTS AND DISCUSSION

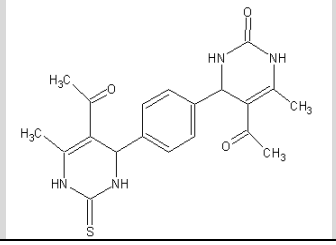
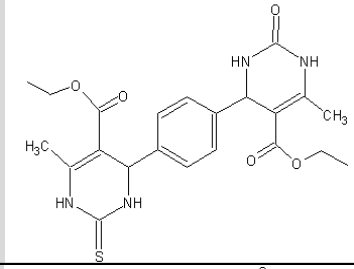
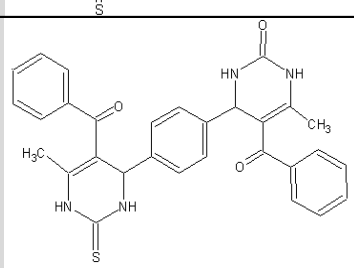
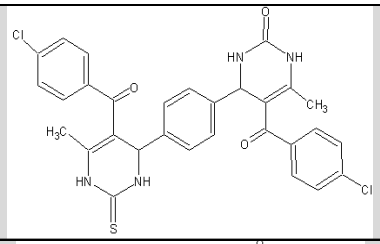
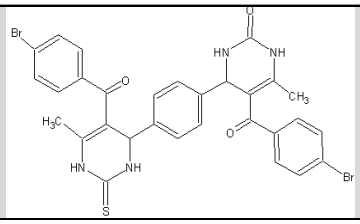
The reaction of dialdehyde (**1**) with β-diketone derivatives (**2a-2e**), urea (**3**) and thiourea (**4**) in the presence of 10 % mol oxalic acid proceeded smoothly in MeCN and was complete within 1 h. Oxalic acid acts as a catalyst in this transformation and the reaction proceeds in the presence of 10 mol % of the catalyst (Table-1).

TABLE-1
YIELDS FOR THE SYNTHESIS OF DIHYDROPYRIMIDINONES WITH DIFFERENT ACIDS

Entry	Catalyst	Yield (%)
1	Orthophosphoric acid	70
2	HCl	75
3	Oxalic acid	83
4	Acetic acid	65

The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of dihydropyrimidin-2(1*H*)-one derivative (**5a-5e**) in 81-88 % yields (Table-2).

TABLE-2
YIELDS FOR THE SYNTHESIZED DIHYDROPYRIMIDINONES UNDER REFLUXING CH_3CN AND OXALIC ACID AS THE CATALYST

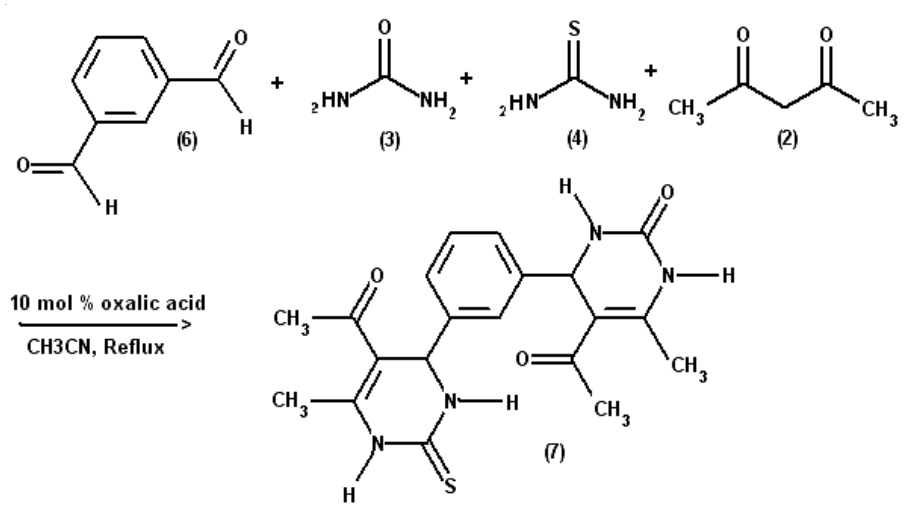
Entry	Product	Yield (%)
5a		83
5b		87
5c		88
5d		83
5e		81

The structures of compounds (**5a-5e**) were deduced from their IR, ^{1}H and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **5a** exhibited four different broad signals for four N-H (δ = 7.77, 9.16, 9.71 and 10.26 ppm) protons. There are two doublets for four protons of aromatic region that shows benzene ring that substituted in para situation. Two different shielded benzilic protons were appeared at 5.11 ppm and 5.21 ppm. The proton-decoupled ^{13}C NMR spectrum of **5a** showed 18 distinct resonances in agreement with the proposed structure. The IR spectrum of **5a** displayed characteristic carbonyl bonds (1660, 1685 and 1690 cm^{-1}) and C=S bonds (1226 cm^{-1}). The mass spectrum of **5a** displayed the molecular ion peak at m/z = 398.

To extend our knowledge of this reaction, we performed the reaction between isophthalic aldehyde (**6**), β-diketones (**2**), urea (**3**) and thiourea (**4**) in the presence of oxalic acid. Similarly, this reaction led to asymmetrically *meta*-substituted dihydropyrimidin-2(1*H*)-one (**7**) (**Scheme-II**).

Conclusion

We have demonstrated the simple and practical synthesis method of asymmetrical branched dihydropyrimidinones from multicomponent reaction of dialdehydes, urea, thiourea and different derivatives of β-diketones under refluxing MeCN. The current method presents a simple and useful synthetic process for asymmetrical branched dihydropyrimidinones



Scheme-II: Reaction of isophthalic aldehyde, urea, tiourea and β-diketones

because of the following advantages: (1) use of cheap and readily available oxalic acid as the catalyst. (2) High yield and short reaction time. (3) Straightforward and easy work-up procedure and last but not least (4) a systematic synthesis method for the compounds containing two different dihydropyrimidinone units that will pave the way of non-symmetrical synthesis method in the immediate future.

ACKNOWLEDGEMENTS

The authors are grateful to Islamic Azad University, South Tehran Branch for financial support.

REFERENCES

1. H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M. Takeda, T. Ishihara, K. Funahashi, F. Satah, M. Morita and T. Noguchi, *J. Med. Chem*., **32**, 2399 (1989).
2. K. Atwal, G.C. Rovnyak, J. Schwartz, S. Moreland, A. Hedberg, J.Z. Gougoutas, M.F. Malley and D.M. Floyd, *J. Med. Chem*., **33**, 1510 (1990).
3. K.S. Atwal, G.C. Rovnyak, S.D. Kimball, D.M. Floyd, S. Moreland, B.N. Swanson, J.Z. Gougoutas, J. Schwartz, K.M. Smillie and M.F. Malley, *J. Med. Chem*., **33**, 2629 (1990).
4. K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg and B.C. O´Reilly, *J. Med. Chem*., **34**, 806 (1991).
5. G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O´Reilly, J. Schwartz and M.F. Malley, *J. Med. Chem*., **35**, 3254 (1992).
6. G.J. Grover, S. Dzwonczyk, D.M. McMullen, C.S. Normadinam, P.G. Sleph and S.J. Moreland, *J. Cardiovasc. Pharmacol*., **26**, 289 (1995); M. Negwer, Organic-Chemical Drugs and their Synonyms; Akademie Verlag: Berlin, p. 2558 (1994).
7. G.C. Rovnyak, S.D. Kimball, B. Beyer, G. Cucinotta, J.D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J.P. McCarthy, R. Zhang and S. Moreland, *J. Med. Chem*., **38**, 119 (1995).
8. D.J. Triggle and S. Padmanabhan, *Chemtracts: Org. Chem*., **8**, 191 (1995).
9. C.O. Kappe, *Tetrahedron*, **49**, 6937 (1993).
10. A.D. Patil, N.V. Kumar, W.C. Kokke, M.F. Bean, A.J. Freyer, C.D. Brosse, S. Mai, A. Truneh, D.J. Faulkner, B. Carte, A.L. Breen, R.P. Hertzberg, R.K. Johnson, J.W. Westley and B.C.M. Potts, *J. Org. Chem*., **60**, 1182 (1995).
11. C.B. Grissom, *Chem. Rev*., **95**, 3 (1995).
12. B.M. Trost, *Science*, **254**, 1471 (1991).
13. R.A. Sheldon, *Chem. Ind*., 903 (1992).
14. B.M. Trost, *Angew. Chem. Int. Ed. Engl*., **34**, 259 (1995).
15. C. Simon, J.-F. Peyronel, F. Clerc and J. Rodriguez, *Eur. J. Org. Chem*., 3359 (2002).
16. A. Dömling and I. Ugi, *Angew. Chem*., **105**, 634 (1993).
17. A. Dömling, E. Herdtweck and I. Ugi, *Acta Chem. Scand*., **52**, 107 (1998).
18. R.V.A. Orru and M. de Greef, *Synthesis*, 1471 (2003).
19. P. Biginelli, *Gazz. Chim.*, **23**, 360 (1893).
20. T. Jin, S. Zhang and T. Li, *Synth. Commun*., **32**, 1847 (2002).
21. S. Tu, F. Fang, S. Zhu, T. Li, X. Zhang and Q. Zhuang, *Synlett*, 537 (2004).
22. P. Salehi, M. Dabiri, M.A. Zolfigol and M.A. Bodaghi Fard, *Tetrahedron Lett*., **44**, 2889 (2003).
23. B. Mirza and J. Azizian, *J. Fluorine Chem*., **129**, 1083 (2008).