AN EFFICIENT AND MODIFIED BIGINELLI-TYPE SYNTHESIS OF 3,4-DIHYDRO-1H-INDENO[1,2-D] PYRIMIDINE-2,5-DIONE USING PHOSPHOROUS PENTOXIDE

Poojali P. Warekar,1 Govind B. Kolekar,2 Madhukar B. Deshmukh,2 and Prashant V. Anbhule2
1Department of Agrochemicals and Pest Management, Shivaji University, Kolhapur, India
2Medicinal Chemistry Research Laboratory, Department of Chemistry, Shivaji University, Kolhapur, India

GRAPHICAL ABSTRACT

Abstract A simple, clean and convenient one-pot method has been developed for the synthesis of 4-phenyl-3,4-dihydro-1H-indeno[1,2-d]pyrimidine-2,5-dione and 4-phenyl-2-thioxo-1,2,3,4-tetrahydro-5H-indeno[1,2-d]pyrimidine-5-one by multicomponent condensation of 1,3-indanedione, aromatic aldehydes and urea/thiourea using phosphorus pentoxide in ethanol under reflux conditions. The simple workup procedure and moderate to good yields within short time are some important features of this protocol. The synthesized compounds have been interpreted on the basis of their spectroscopic data.

Keywords Biginelli reaction; dihydropyrimidones; phosphorous pentoxide

Received May 19, 2014.
Address correspondence to Prashant V. Anbhule, Medicinal Chemistry Research Laboratory, Department of Chemistry, Shivaji University, Kolhapur 416004, India. E-mail: pvanbhule2011@gmail.com
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
INTRODUCTION

Nitrogen-containing heterocyclic compounds show significant and precious biological activities.\(^1\) In the past two decades, the synthesis of dihydropyrimidones (DHPMs) and their analogs have gained considerable attention as synthetic targets for researchers because of their valuable and significant biological activities such as antibacterial,\(^2\) antiviral,\(^3\) anti-inflammatory,\(^4\) antihypertensive,\(^5\) antitumor,\(^6\) \(\alpha\)-adrenergic antagonist,\(^7\) and HIV-gp-120-CD4-inhibitory\(^8\) activities. It has very broad spectrum of biological activities.\(^9\) Moreover, DHPMs have been recently recognized as imperative drugs in antihypertensive treatment and as calcium channel blockers\(^10\) and neuropeptide Y antagonists.\(^11\)

Some of the analogues of DHPMs have been used as active ingredients in drugs. Compound (I) is a potent calcium channel blockers,\(^12\) whereas compound (II) has excellent anticancer activity.\(^13\)

The first synthesis of DHPM was reported by an Italian chemist, Pietro Biginelli, in 1893, using a one-pot cyclocondensation of aromatic aldehydes, ethyl aceto acetate and urea in the presence of strong mineral acid.\(^14\) This original reaction suffered from drawbacks such as poor yields and longer reaction time, especially with aliphatic aldehydes.

Because of the vital significance in the medicinal field, DHPMs are probes for a wide range of pharmaceuticals and other biosignificant molecules. Consequently, a systematic pursuit has been led by current researchers to innovate and develop the methodological approach in regards of yield, reaction time and catalyst. Efforts made in the methodological enhancement for the synthesis of DHPMs promoted the use of various kinds of catalysts,\(^15-18\) multistep synthesis,\(^19\) microwave irradiation,\(^20\) ultrasound irradiation\(^21\) and ionic liquids.\(^22\)

Multicomponent reactions (MCR) that employ three or more reactants combined in one pot have considerable importance as compared to the conventional multistep route as they furnish convenient isolation of complex molecules without any separation of intermediate during the reaction process.\(^23\) These features are important in the early step of drug discovery to screen biological activities\(^24\) and
have led to widespread application of MCRs for the modern demands of the contemporary organic chemistry\cite{25–30} for example, by using different kinds of 1,3-dicarbonyl compounds for generation of a new library of DHPM-like derivatives to find potent new bioactive compounds.

The encouraging reports on the smooth working of \( \text{P}_2\text{O}_5 \) in the organic transformations\cite{31} and the initial successful incorporation of phosphorous pentoxide for the original Biginelli condensation\cite{32} prompted us to extend its use for the Biginelli-like condensation of 1,3-indanedione, aromatic aldehydes, and urea/thiourea to get 4-aryl-3,4-dihydro-1H-indeno[1,2-d]pyrimidine-2,5-dione and 4-aryl-2-thioxo-1,2,3,4-tetrahydro-5H-indeno[1,2-d]pyrimidine-5-one.

A literature survey reveals only one report available on the synthesis of indeno[1,2-d]pyrimidines\cite{33} which involves one-pot condensation of benzaldehyde, 1,3-indanedione and urea/thiourea. This reported method has its own merits and demerits. To establish a convenient and highly proficient synthetic methodology for the preparation of these vital structural motifs while evading the problems of the previous reports, and in the continuation of our efforts to develop newer synthetic methodologies\cite{34} we put forth an efficient synthetic route for obtaining 3,4-dihydro-1H-indeno[1,2-d]pyrimidine-2,5-dione using phosphorous pentoxide through a one-pot MCR (Scheme 1).

\section*{RESULTS AND DISCUSSION}

Initially, 1,3-indanedione (0.14 g, 1 mmol), 2-hydroxy benzaldehyde (0.12 g, 1 mmol) and urea (0.30 g, 5 mmol) using catalytic amount of phosphorous pentoxide were refluxed on a water bath. After the completion of the reaction, as monitored by thin-layer chromatography (TLC), the mixture was poured on crushed ice with constant stirring. The extruded product that separated out was filtered and successively washed with aqueous ethanol to remove the unconsumed 1,3-indanedione impurity.

Phosphorous pentoxide is an inexpensive reagent that is effective for the progress of the reaction. Phosphorus pentoxide acts as an acid catalyst and increases the acidic conditions in the reaction, which leads shorter reaction time.\cite{35} It is a good dehydrating reagent, soluble in water and easily removed. The formed products were recrystallized from ethanol and analyzed by spectroscopic data. The IR spectrum of 4-(2-hydroxyphenyl)-3,4-dihydro-1H-indeno[1,2-d]pyrimidine-2,5-dione (Table 3, entry 1) shows absorption at 1637, 1701, 3251, and 3407 cm\(^{-1}\) whereas the \( ^1\text{H} \)
NMR of the same compound exhibits a singlet at $\delta$ 5.52 due to methine proton, two broad singlets at $\delta$ 7.96 due to the two –NH protons and eight aromatic protons as multiplets between $\delta$ 6.67 and 7.56. The broad singlet at $\delta$ 10.60 is due to phenolic –OH. The obtained spectroscopic data and reported literature values were found to be in good agreement with proposed structure. This initial result inspired us to study this reaction in detail.

Therefore, to investigate the efficiency of catalyst, the same reaction (Scheme 1) was extended for various catalysts such as Na$_2$CO$_3$, Na$_2$SO$_4$, Cu nanoparticle and P-TSA. The details of these studies are summarized in Table 1.

The results obtained for the catalytical evaluation proved that P$_2$O$_5$ is an excellent agent which gave the desired product in good to excellent yields with considerable shortening in the reaction time.

Propelled by these encouraging results, optimization of required catalytical amount (Table 2) was carried out for the same trial reaction by varying the quantities of phosphorus pentoxide.

As per our investigation, it has been concluded that 200 mg of phosphorus pentoxide is sufficient quantity for the reaction to get maximum yield of the product. On further addition of catalyst, there is no any change in the yield or time of the reaction.

The solvent efficiency for the same protocol was evaluated by altering the solvent with water; however, the desired reaction failed to proceed beyond the Knoevenagel formation. Consequently ethanol was considered the appropriate solvent, affording resultant dihydropyrimidones in excellent yield. To assess the versatility of the method using optimum quantity of catalyst (Table 2, entry 4), the reaction was extended to variety of aromatic and aliphatic aldehydes with simultaneous variation in the urea derivatives. Regardless of the varied alterations made in the respective reactants the protocol yielded similar products in good to excellent yields. Moreover, both electron-donating and electron-withdrawing aldehydes have given good to excellent yields of the product. All these results are summarized in Table 3.

| Table 1. Optimization of reaction conditions |
|---------------------------------------------|
| Entry | Catalyst       | Solvent | Time (h) | Yield (%) |
|-------|----------------|---------|----------|-----------|
| 1.    | Na$_2$CO$_3$   | Ethanol | 8        | —         |
| 2.    | Na$_2$SO$_4$   | Ethanol | 8        | —         |
| 3.    | Cu nanoparticle| Ethanol | 9        | —         |
| 4.    | P-TSA          | Ethanol | 8        | —         |
| 5.    | Cu nanoparticle| Water   | 9        | —         |
| 6.    | Phosphorous pentoxide | Ethanol | 4–6      | 80–95     |

| Table 2. Optimization of phosphorus pentoxide |
|-----------------------------------------------|
| Entry | Quantity of P$_2$O$_5$ (mg) | Time (h) | Yield (%) |
|-------|-----------------------------|----------|-----------|
| 1.    | 40                          | 7.0      | 60        |
| 2.    | 60                          | 5.0      | 70        |
| 3.    | 100                         | 5.0      | 80        |
| 4.    | 200                         | 4–6      | 80–95     |
The plausible mechanism for the formation of 4-phenyl-3,4-dihydro-1H-indeno[1,2-d] pyrimidine-2,5-dione and 4-phenyl-2-thioxo-1,2,3,4-tetrahydro-5H-indeno[1,2-d] pyrimidine-5-one is shown in Scheme 2. The reaction may proceed through the condensation of 1,3-indanedione 1 with aldehyde 2 to give Knoevenagel product 3. The Michael addition of urea/thiourea 4 takes place on the Knoevenagel product followed by successive cyclization and dehydration of 5 provide desired product 6. The essential role of phosphorus pentoxide in this reaction to act as an acid catalyst and dehydrating reagent, which not only increases the rate of the reaction but it also helps cyclization to get the desired product (Scheme 2).

Table 3. Data for the synthesis of dihydropyrimidinones in the presence of phosphorus pentoxide

| Entry | R           | X | Time (h) | Yield (%) | Mp obs. (°C) |
|-------|-------------|---|----------|-----------|--------------|
| 1     | 2-(OH)-C₆H₄ | O | 4        | 83        | 196–200 (200–204)³³³ |
| 2     | 4-(Cl)-C₆H₄ | O | 4        | 94        | 216–217 (215–217)³³³ |
| 3     | 4-(OCH₃)-C₆H₄| O | 5        | 87        | 179–183 (180–183)³³³ |
| 4     | C₆H₆        | O | 6        | 83        | 173–175 (175–178)³³³ |
| 5     | 4-(OH),3-(OCH₃)-C₆H₃ | O | 5        | 90        | 221–223 (220–223)³³³ |
| 6     | 3-(NO₂)-C₆H₄ | O | 5        | 93        | 200–204        |
| 7     | 4-(OH)-C₆H₄ | O | 5        | 88        | 250–255        |
| 8     | 2-(OH)-C₆H₄ | S | 4        | 84        | 240–244 (240–243)³³³ |
| 9     | 4-(Cl)-C₆H₄ | S | 5        | 91        | 183–185 (185–187)³³³ |
| 10    | 4-(OCH₃)-C₆H₄| S | 4        | 85        | 144–148 (144–147)³³³ |
| 11    | C₆H₆        | S | 6        | 82        | 250–252 (249–252)³³³ |
| 12    | 4-(OH),3-(OCH₃)-C₆H₃ | S | 6        | 92        | 194–196 (196–198)³³³ |
| 13    | 4-(OH)-C₆H₄ | S | 4        | 81        | 245–250        |
| 14    | nC₆H₇      | O | 4        | —         | —             |
| 15    | nC₅H₁₁     | O | 5        | —         | —             |

Scheme 2. Plausible mechanism of the reaction.
CONCLUSION

We have successfully developed simple, clean and rapid method for the synthesis of 3,4-dihydro-1H-indeno[1,2-d]pyrimidine-2,5-dione derivative using phosphorous pentoxide, which is an efficient and inexpensive reagent. The phosphorous pentoxide greatly assists the reaction, which is a one-step synthesis of Biginelli-like DHPMs in good to excellent yields. The synthesized compounds may have very broad scope in biological investigations.

EXPERIMENTAL

The melting points were determined in an open capillary and were uncorrected. The purity of sample was checked by thin-layer chromatography (TLC) using silica gel 60-F 254 plates. The reported compounds were confirmed by $^1$H NMR and IR while unreported compounds were confirmed by $^1$H NMR, IR, $^{13}$C NMR and mass analysis. The $^1$H NMR and $^{13}$C NMR spectra were taken in dimethylsulfoxide (DMSO-$d_6$) using Bruker 300- and 75-MHz instruments or Bruker 400- and 100-MHz spectrophotometer with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on a Shimadzu IR-450 FT-IR spectrophotometer. All the data agreed with the proposed structure.

General Procedure for Synthesis of 3,4-Dihydropyrimidin-2(1H)-one

1,3-Indanedione (1 mmol), aromatic/aliphatic aldehydes (1 mmol), urea/thiourea (5 mmol) and phosphorous pentoxide (0.2 g) in a 25-ml round-bottomed flask were mixed thoroughly and refluxed on a water bath using ethanol as a solvent. The reaction was completed within 4–5 h as monitored by TLC. After completion, the mixture was cooled and poured on the crushed ice. On stirring, the desired product was separated. The separated product was then filtered, washed with water and petroleum ether, dried and recrystallized using ethanol to get the pure product.

4-(2-Hydroxyphenyl)-3,4-dihydro-1H-indeno[1,2-d]pyrimidine-2,5-dione (Entry 1)

Orange solid, mp 196–200 °C (lit. 200–204$^{[33]}$), yield (83%); IR (KBr): 1637, 1701, 3251, 3407 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 5.52 (s, 1H, -CH), 6.67–6.72 (m, 1H, $H_{Ar}$), 6.77–6.80 (d, 1H, $H_{Ar}$), 7.00–7.04 (m, 2H, $H_{Ar}$), 7.20–7.33 (m, 3H, $H_{Ar}$), 7.54–7.56 (m, 1H, $H_{Ar}$), 7.96 (br.s, 2H, -NH), 10.60 (s, 1H, -OH). Elemental anal. found: C, 69.78%; H, 4.08%; N, 9.47%. Calcd. for C$_{17}$H$_{12}$N$_2$O$_3$: C, 69.86%; H, 4.14%; N, 9.58%.

FUNDING

P. P. W. thanks the Department of Science and Technology, New Delhi, for an INSPIRE Fellowship (No. DST/INSPIRE Fellowship/2013/197) and P. V. A. acknowledges the University Grants Commission, New Delhi, for sanctioning a major research project [F. No. 39-786/2010(SR)].
SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

REFERENCES

1. Gilchrist, T. L. *Heterocyclic Chemistry*. 3rd ed.; Prentice Hall: Upper Saddle River, NJ, 1997.
2. Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis*. 1999, 1799.
3. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; et al. *J. Org. Chem.* 1995, 60, 1182.
4. Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altinok, G. *Farmaco*. 2002, 57, 101.
5. Grover, G. J.; Dzwonczyk, S.; McMulten, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P. G.; Moreland, S. *J. Cardiovas. Pharmacol.* 1995, 26, 289.
6. Kappe, C. O. *Tetrahedron*. 1993, 49, 6937.
7. (a) Sidler, D. R.; Larsen, R. D.; Chartrain, M.; Ikemoto, N.; Roberg, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. PCT International Patent WO 9907695, 1999; (b) Sidler, D. R.; Larsen, R. D.; Chartrain, M.; Ikemoto, N.; Roberg, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. *Chem. Abstr.* 1999, 130, 182478.
8. Snider, B. B.; Shi, Z. *J. Org. Chem.* 1993, 58, 3828.
9. Chen, Q.; Jiang, L.-L.; Chen, C.-N.; Yang, G.-F. *J. Heterocycl. Chem.* 2009, 46, 139.
10. (a) Atwal, K. S.; Moreland, S. *Bioorg. Med. Chem. Lett.* 1991, 1, 291; (b) Ronyak, G. C.; Kinball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* 1995, 38, 119.
11. Bruce, M. A.; Pointdexter, G. S.; Johnson, G. PCT International WO Patent 9833791, 1998; (b) Bruce, M. A.; Pointdexter, G. S.; Johnson, G. *Chem. Abstr.* 1998, 129, 148989.
12. (a) Atwal, K. S.; Ronyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. *J. Med. Chem.* 1990, 33, 1510; (b) Zorkun, I. S.; Sarac, S.; Celebib, S.; Erolb, K. *Bioorg. Med. Chem.* 2006, 14, 8582; (c) Chikhale, R. V.; Bhole, R. P.; Khedekar, P. A.; Semus, S. F.; Evans, C.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R. *J. Med. Chem.* 2008, 51, 6631.
13. (a) Klein, E.; DeBonis, S.; Thiede, B.; Skoufias, D. A.; Kozielski, F.; Lebeaua, L. *Bioorg. Med. Chem.* 2007, 15, 6474; (b) Kaan, H. Y. K.; Ulaganathan, V.; Rath, O.; Prokopcov, H.; Dallinger, D.; Kappe, C. O.; Kozielski, F. *J. Med. Chem.* 2010, 53, 5676; (c) Wright, C. M.; Chovatiya, R. J.; Jameson, N. E.; Turner, D. M.; Zhu, G.; Werner, S.; Huryn, D.; Papas, M.; Billy, J. M.; Day, W.; Wip P.; Brodskya, J. L. *Bioorg. Med. Chem.* 2008, 16, 3291; (d) Agbaje, O. C.; Fadeyi, O. O.; Fadeyi, S. A.; Myles, L. E.; Okoro, C. O. *Bioorg. Med. Chem. Lett.* 2011, 21, 989; (e) Kumar, B. R. P.; Sankar, G.; Baig, R. B. N.; Chandrashekaran, S. *Eur. J. Med. Chem.* 2009, 44, 4192; (f) Ibrahim, D. A.; El-Metwally, A. M. *Eur. J. Med. Chem.* 2010, 45, 1158.
14. Biginelli, P. *Gazz. Chim. Ital.* 1893, 23, 360.
15. Saini, A.; Kumar, S.; Sandhu, J. S. *Indian J. Chem. Sec. B.* 2006, 45, 684.
16. Gourhari, M.; Pradip, K.; Chandrani, G. *Tetrahedron Lett.* 2003, 44, 2757.
17. Lu, J.; Ma, H. *Synlett.* 2000, 1, 63.
18. Yadav, J. S.; Reddy, B. V. S.; Shrinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis.* 2001, 9, 1341.
19. Fadda, A. A.; Bondock, S. B.; Khalil, A. M.; Tawfik, E. H. *J. Heterocycl. Chem.* 2013, 50, 838.
20. Banerjee, K.; Mitra, A. K. *J. Indian Chem. Soc.* 2003, 80, 51.
21. Li, J. T.; Han, J. F.; Yang, J. H.; Li, T. S. *Ultrason Sonochem.* 2003, 10, 119.
22. Peng, J. J.; Deng, Y. Q. *Tetrahedron Lett.* 2001, 42, 5917.
23. Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* 2004, 45, 8625.
24. Patrick, G. L. *An Introduction to Medicinal Chemistry*; Oxford University Press: New York, 2005.
25. Pandey, J.; Anand, N.; Tripathi, R. P. *Tetrahedron.* 2009, 65, 9350–9356.
26. Murata, H.; Ishitani, H.; Iwamoto, M. *Org. Biomol. Chem.* 2010, 8, 1202–1211.
27. Ryabukhin, S. V.; Plaskon, A. S.; Bondarenko, S. S.; Ostapchuk, E. N.; Grygorenko, O. O.; Shishkin, O. V.; Tolmachev, A. A. *Tetrahedron Lett.* 2010, 51, 4229–4232.
28. Wang, Z.; Xu, Li.; Xia, C.; Wang, H. *Tetrahedron Lett.* 2004, 45, 7951–7953.
29. Figueroa-Valverde, L.; Diaz-Cedillo, F.; Camacho-Luis, A. *Monatsh Chem.* 2010, 141, 75–78.
30. Phucho, I. T.; Nongpiur, A.; Nongrum, R.; Nongkhlaw, R. L. *Indian J. Chem. Sec. B.* 2010, 49(3), 346–350.
31. Nalage, S. V.; Bhosale, S. V.; Bhosale, D. S.; Jadhav, W. M. *Chin. Chem. Lett.* 2010, 21, 790–793.
32. Deshmukh, M. B.; Anbhule, P. V.; Jadhav, S. D.; Mali, A. R.; Jagtap, S. S.; Deshmukh, S. A. *Indian J. Chem.* 2007, 46B, 1545.
33. Dabhakar, V. V.; Patil, S. R.; Pandey, R. V. *J. Heterocycl. Chem.* 2012, 49, 929.
34. (a) Deshmukh, M. B.; Salunkhe, S. M.; Patil, D. R.; Anbhule, P. V. *Eur. J. Med. Chem.* 2009, 44, 2651; (b) Patil, D. R.; Salunkhe, S. M.; Deshmukh, M. B.; Anbhule, P. V. *J. Heterocycl. Chem.* 2011, 48, 1414; (c) Patil, D. R.; Salunkhe, S. M.; Deshmukh, M. B.; Anbhule, P. V. *J. Heterocycl. Chem.* 2011, 48, 134.
35. Kumar, R.; Raghuvanshi, K.; Verma, R. K.; Singh, M. S. *Tetrahedron Lett.* 2010, 51, 5933–5936.