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Biginelli reaction beyond three-component limit: synthesis of functionalized pyrimidinones via a one-pot Biginelli-Pd mediated C–C coupling strategy

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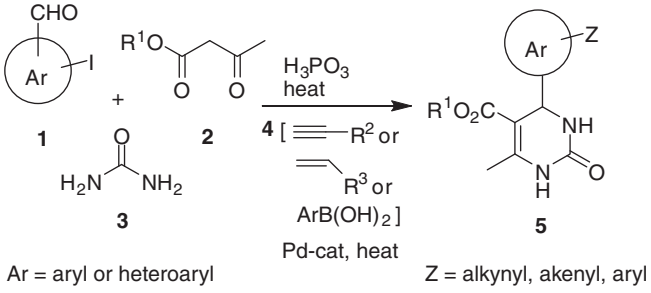
ABSTRACT

A new and one-pot synthesis of novel alkynyl/alkenyl/aryl (hetero)aryl substituted 3,4-dihydropyrimidin-2(1*H*)-one derivatives has been developed via a multi-component reaction involving sequential phosphorus acid-mediated solvent-free Biginelli followed by copper-free Sonogashira or Heck or Suzuki reaction.

Multi-component reactions (MCRs) are powerful strategies for the quick synthesis of diverse and complex organic molecules of potential interest particularly in the area of material science and drug discovery.[1] This methodology allows creation of diversity in addition to molecular complexity by the facile formation of several new covalent bonds in a one-pot transformation. The search and discovery of new MCRs, therefore, have gained tremendous importance.[2] One of the widely used MCRs, known as Biginelli reaction[3] involves the cyclocondensation of an aldehyde, a β-ketoester, and urea (or thiourea) to give dihydropyrimidin-2(1*H*)-ones (or thio analogues) of pharmacological importances.[4,5] The alkynylation of the (hetero)arene, that is, the Sonogashira reaction[6] on the other hand has been termed as a booming methodology[7a] in organic synthesis because of its remarkable applications in C–C bond forming reactions under Pd–Cu catalysis. A Cu-free Sonogashira coupling[8] is of particular value as it reduces the dimerization of reactant alkynes significantly, thereby avoiding a cumbersome purification process. The Heck and Suzuki reactions are other C–C bond forming reactions that have found wide applications.[7b,c] While an impressive number of reports are now available on Biginelli reaction[9] to improve the reaction conditions and product yields along with variations in all the three reactants, its further application beyond the three component limit has not been explored. The present communication describes an overall four component reaction involving a sequential phosphorus acid-mediated Biginelli followed by Cu-free Sonogashira or Heck or Suzuki reaction. This MCR is particularly attractive, because by choosing an appropriate aldehyde along with an alkyne/alkene/aryl boronic acid partner, a dihydropyrimidinone can be easily synthesized possessing functionalized (hetero)arene group of specific interest at C-4 (Scheme 1).

Recently, we have reported a Pd-catalyzed one-pot multi-component coupling reaction for the construction of benzene ring fused with a carbocycle or heterocycle particularly under a Cu-free



Scheme 1. MCR involving Biginelli followed by Pd-catalyzed C–C bond forming reaction in tandem.

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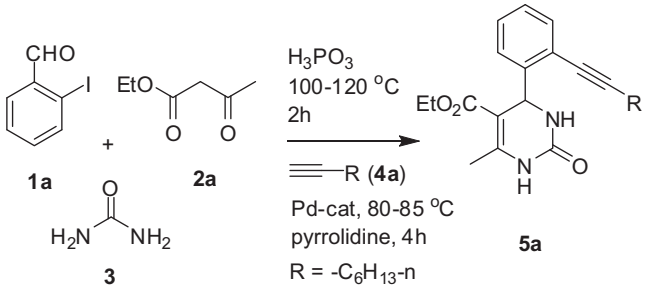
Table 1
The reaction of *o*-iodobenzaldehyde **1a**, the β-ketoester **2a**, urea **3,** and terminal alkyne **4a**[a]



Entry	H_3PO_3 (mol %)	Pd-cat (mol %)	%Yield[b]
1	1.0	$(PPh_3)_2PdCl_2$ (2.0)	35
2	2.5	$(PPh_3)_2PdCl_2$ (2.0)	46
3	5.0	$(PPh_3)_2PdCl_2$ (2.0)	59
4	7.5	$(PPh_3)_2PdCl_2$ (2.0)	68
5	10.0	$(PPh_3)_2PdCl_2$ (2.0)	87
6	20.0	$(PPh_3)_2PdCl_2$ (2.0)	86
7	10.0	$(PPh_3)_2PdCl_2$ (1.0)	64
8	10.0	$PdCl_2$ (2.0)	81

[a] All the reactions were carried out using **1a** (1.0 mmol), **2a** (5.0 mmol), **3** (1.25 mmol), and H_3PO_3 in neat at 100–120 °C followed by the addition of pyrrolidine (3.0 mL), Pd-catalyst and **4a** (1.2 mmol) at 80–85 °C.
[b] Isolated yield.

condition.[10] More recently, we have observed that 3,4-dihydropyrimidin-2(1*H*)-one possessing an iodoarene moiety at C-4 undergoes Pd-mediated smooth coupling reaction with terminal alkynes in the absence of Cu-salt. This prompted us to examine the in situ generation of iodide partner via Biginelli reaction. Our objective was twofold, for example, (i) identification of a suitable Biginelli catalyst compatible for subsequent transformation in the same pot, (ii) to establish an appropriate reaction condition for efficient Sonogashira/Heck/Suzuki coupling to complete the procedure. Initially, we focused on Biginelli–Sonogashira reaction. To our satisfaction, the phosphorus acid[9j] was found to be a new and effective catalyst for the Biginelli step whereas the use of Cu-salt in the Sonogashira step was counter productive. Thus, we examined the reaction of *o*-iodobenzaldehyde **1a**, the β-ketoester **2a**, urea **3** and then terminal alkyne **4a** under various conditions to find the optimum condition for obtaining the MCR product in good yield (Table 1). Initially, the reaction was carried out using various amounts of H_3PO_3 (1–20 mol %) followed by $(PPh_3)_2PdCl_2$ (2 mol %) (Table 1, entries 1–6). While the expected product **5a** was isolated in all these cases the best result, howeve,r was achieved when 10.0 mol % of H_3PO_3 was used in combination with 2 mol % of $(PPh_3)_2PdCl_2$ (Table 1, entry 5). The use of increased amount of H_3PO_3 did not enhance the product yield (Table 1,entry 6) though the reaction was faster, whereas a lower quantity of Pd catalyst decreased the yield (Table 1,entry 7). The catalyst $PdCl_2$ was found to be equally effective (Table 1,entry 8). Notably, the Biginelli step was carried out under a solvent-free condition, whereas pyrrolidine was used as a base as well as a solvent for the Cu-free Sonogashira coupling step. The use of other bases such as, Et_3N and diisopropylethyl amine was also investigated and was found to be effective. However, the best yield of the product was achieved by using pyrrolidine. The compound **5a** was well characterized by IR absorbsions at 2227 (—C≡C—), 1700 (C=O)

Table 2
Synthesis of 2-alkynylphenyl substituted dihydropyrimidin-2(1*H*)-one derivatives (**5a–m**) using the aldehyde **1a**[a]

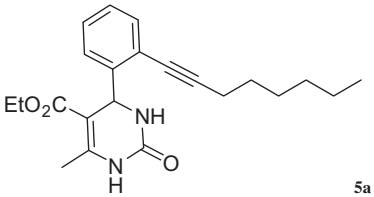
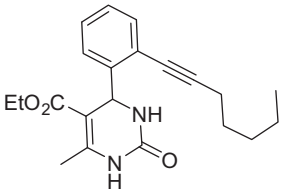
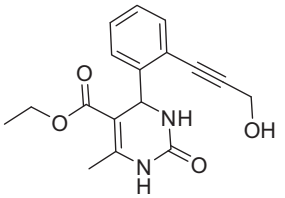
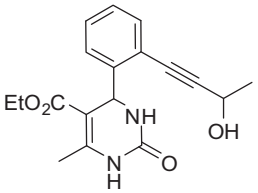
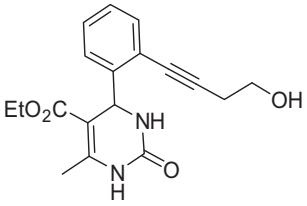
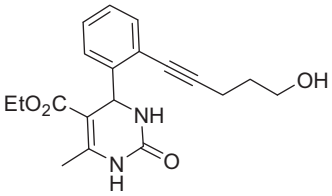
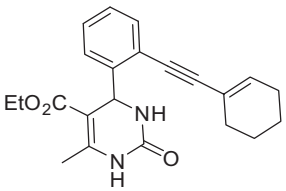
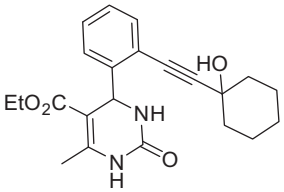
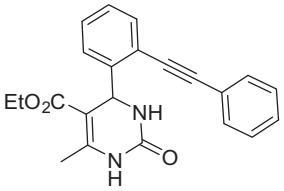
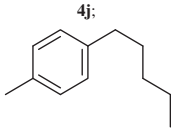
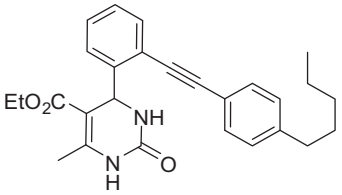
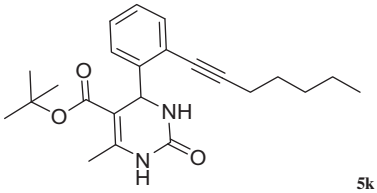
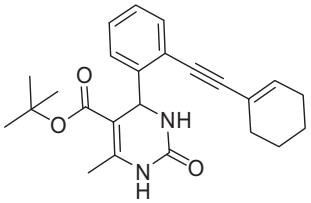
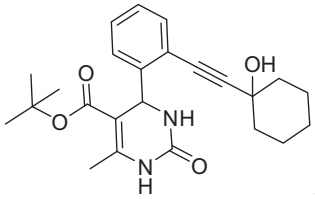
Entry	Ester **2**; R^1	Alkyne **4**; R^2	Product (**5**)	Time[b] (h)	%Yield[c]
1	**2a**; Et	**4a**; *n*-Hexyl	 **5a**	1.0	87
2	**2a**	**4b**; *n*-Pentyl	 **5b**	1.0	88
3	**2a**	**4c**; $-CH_2OH$	 **5c**	1.5	85
4	**2a**	**4d**; $-CH(OH)CH_3$	 **5d**	1.5	83

Table 2 (*continued*)

Entry	Ester **2**; R^1	Alkyne **4**; R^2	Product (**5**)	Time[b] (h)	%Yield[c]
5	**2a**	**4e**; $-(CH_2)_2OH$	 **5e**	1.5	82
6	**2a**	**4f**; $-(CH_2)_3OH$	 **5f**	1.5	83
7	**2a**	**4g**; 	 **5g**	1.0	89
8	**2a**	**4h**; 	 **5h**	1.5	84
9	**2a**	**4i**; 	 **5i**	1.5	82
10	**2a**	**4j**; 	 **5j**	1.5	84
11	**2b**; *t*-Bu	**4b**	 **5k**	1.0	86
12	**2b**	**4g**	 **5l**	1.0	85

(*continued on next page*)

Table 2 (*continued*)

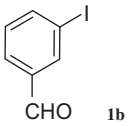
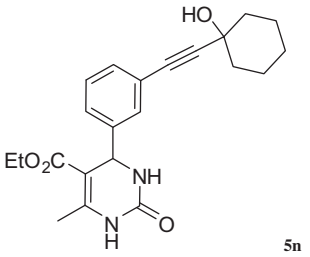
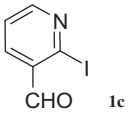
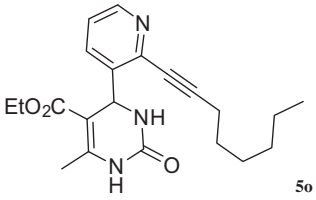
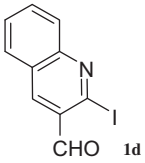
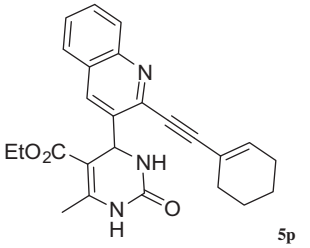
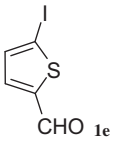
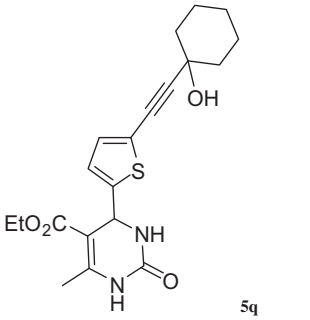
Entry	Ester **2**; R^1	Alkyne **4**; R^2	Product (**5**)	Time[b] (h)	%Yield[c]
13	**2b**	**4h**	 **5m**	1.5	83

[a] All the reactions were carried out using **1a** (1.0 mmol), **2** (5.0 mmol), **3** (1.25 mmol) and H_3PO_3 (10 mol %) in neat at 100–120 °C followed by addition of pyrrolidine(3.0 mL), $(PPh_3)_2PdCl_2$ (2 mol %) and **4** (1.2 mmol) at 80–85 °C.
[b] For Sonogashira step.
[c] Isolated yield.

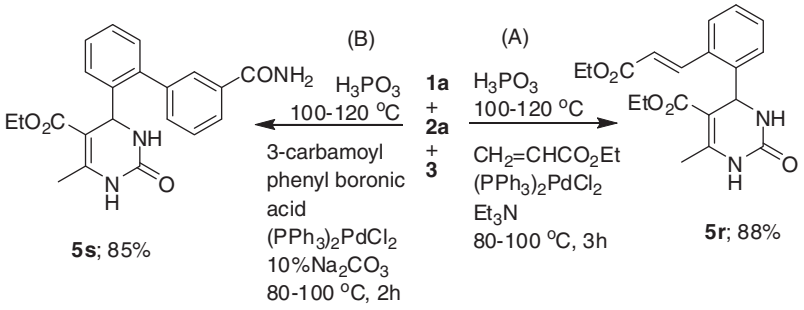
and 1650 (C=O) cm^{-1} and the appearance of a peak at 5.6 δ corresponding to C-4 hydrogen.[11]

We were pleased to find that the four-component reaction provided dihydropyrimidinones with a range of aryl substitution patterns at C-4 (Table 2). The one-pot Biginelli–Sonogashira reaction proceeded well with a variety of terminal alkynes to give **5** in good yields (Table 2, entries 1–13). A range of substituents including alkyl, hydroxyalkyl, cycloalkyl, or aryl

Table 3
Synthesis of alkynyl(hetero)aryl substituted dihydropyrimidin-2(1*H*)-one derivatives (**5n**–**q**) using ester **2a** and various aldehydes (**1b**–**e**)[a]

Entry	Aldehyde (**1**)	Alkyne (**4**)	Product (**5**)	Time[b] (h)	%Yield[c]
1	 **1b**	**4h**	 **5n**	1.5	80
2	 **1c**	**4a**	 **5o**	1.5	80
3	 **1d**	**4g**	 **5p**	2.0	82
4	 **1e**	**4h**	 **5q**	2.0	81

[a] All the reactions were carried out using **1** (1.0 mmol), **2a** (5.0 mmol), **3** (1.25 mmol), and H_3PO_3 (10 mol %) in neat at 100–120 °C followed by addition of pyrrolidine (3.0 mL), $(PPh_3)_2PdCl_2$ (2 mol %) and **4** (1.2 mmol) at 80–85 °C.
[b] For Sonogashira step.
[c] Isolated yield.



Scheme 2. MCR involving Biginelli–Heck (A) and Biginelli–Suzuki (B) reaction.

present in the alkyne component were found to be well tolerated. It is worth mentioning that the present four-component reaction was carried out in open air under normal atmospheric pressure.

We have shown that a variety dihydropyrimidinones can be prepared via Biginelli–Sonogashira reaction in a single pot. The optimized condition was used to create further diversity at C-4. Thus various aryl and heteroaryl aldehydes were used to give the desired products in good yields (Table 3).

We then focused on combining Biginelli reaction with other Pd-catalyzed C–C bond forming reactions such as Heck[12] or Suzuki[13] coupling. Accordingly, ethyl acrylate and 3-carbamoyl phenyl boronic acid was used in the MCR reaction of **1a**, **2a,** and **3** (Scheme 2)**.** Under suitable reaction conditions the desired product corresponding to Biginelli–Heck (**5r**) and Biginelli–Suzuki (**5s**) was obtained in good yield. Similarly, the use of **1b** in Biginelli–Suzuki reaction provided the regio-isomer (**5t**) of **5s** (see ESI). Mechanistically, the MCR described here proceeds via H_3PO_3-mediated Biginelli reaction to generate the desired iodopyrimidinone intermediate in situ that undergoes C–C bond formation under Pd-catalysis. The H_3PO_3 perhaps activates the carbonyl group[4,14] of the aldehyde, thereby facilitating the reaction with urea and ester. Nevertheless, to gain further evidence we conducted the condensation reaction of **1a**, **2a,** and **3** in the presence of H_3PO_3. The corresponding *o*-iodophenyl substituted 3,4-dihydropyrimidin-2(1*H*)-one isolated was then treated separately with the terminal alkyne **4a** and $(PPh_3)_2PdCl_2$ in pyrrolidine under a Cu-free condition. The desired product **5a** was isolated in good yield indicating that the present single-pot four component reaction proceeds via iodo(hetero)aryl substituted 3,4-dihydropyrimidin-2(1*H*)-one.

In conclusion, we have demonstrated the first multi-component reaction involving sequential phosphorus acid-mediated solvent-free Biginelli reaction followed by copper-free Sonogashira/Heck/Suzuki coupling leading to the formation of novel 3,4-dihydropyrimidin-2(1*H*)-one derivatives in a single pot. Since the quest for these types of new synthetic concepts is high the methodology, therefore, would find wide application in combinatorial and diversity-oriented synthesis of dihydropyrimidones of potential pharmacological interest.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.015.

References and notes

1. Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
2. Weber, L.; Lllgen, K.; Almstetter, M. *Synlett* **1999**, 366.
3. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
4. For a review, see: (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. and references cited therein; (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.
5. (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629; (b) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J. Z.; Hedberg, A.; Malley, M. F.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119. and references cited therein.
6. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
7. (a) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874; (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry A Guide For the Synthetic Chemist*, 2nd edn.; Elsevier: Oxford, 2006; (c) Tsuji, J. *Palladium in Organic Synthesis*, 1st edn.; Berlin: Springer, 2005.
8. Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, 1976.
9. (a) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957; (b) Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454; (c) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718; (d) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270; (e) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864; (f) Lu, J.; Ma, H. *Synlett* **2000**, 63; (g) Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465; (h) Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657; (i) Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305; For Biginelli reaction using chiral phosphoric acid, see: (j) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802.
10. Swamy, N. K.; Tatini, L. K.; Babu, J. M.; Annamalai, P.; Pal, M. *Chem. Commun.* **2007**, 1035.
11. A typical procedure for the preparation of **5a**: To a mixture of aldehyde **1a** (1.0 mmol), ethyl acetoacetate **2a** (5.0 mmol), and urea **3** (1.25 mmol) was added H_3PO_3 (10 mol %) at room temperature. After stirring for 5 min, the reaction flask was fitted with a condenser for cold water circulation and the mixture was heated to 100–120 °C for 1.0 h and then cooled to 50 °C. To this was added pyrrolidine (3 mL), $PdCl_2(PPh_3)_2$ (2 mol %) and the alkyne (**4a**) with stirring. The mixture was stirred at 80–85 °C for 1.0 h cooled to room temperature, poured into water (25 mL), and extracted with ethyl acetate (3 × 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography using petroleum ether–EtOAc to give the compound **5a** as light brown solid, mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (bs, 1H, NH), 7.40 (d, J = 5.5 Hz, 1H, arom H), 7.23-7.14 (m, 3H, arom H), 5.88 (bs, 1H, NH), 5.6 (s, 1H, CH), 4.02 (q, J = 6.9 Hz, 2H, OCH_2), 2.46 (t, J = 6.9 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 1.62-1.31(m, 8H, CH_2), 1.05 (t, J = 6.9 Hz, 3H, CH_3), 0.90 (t, J = 6.9 Hz, 3H, CH_3); ^{13}CNMR ($CDCl_3$, 50 MHz): δ 165.5, 153.3, 148.2, 143.7, 132.6, 128.2, 127.6, 125.7, 122.3, 98.9, 95.5, 78.2, 59.8, 53.2, 31.3, 29.7, 28.7, 22.6, 19.6, 18.2, 14.0; IR (KBr, cm^{-1}): 3226, 2931, 2227, 1700, 1650; HRMS (ESI): calcd for $C_{22}H_{29}N_2O_3$ $(M+H)^+$ 369.2178, found 369.2166.
12. (a) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320; (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
13. Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866.
14. Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.