RSC Advances

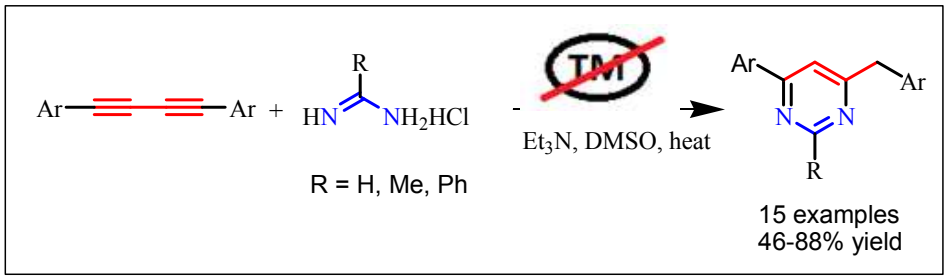
ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Graphical Abstract

Transition metal free synthesis of 2,4,6-trisubstituted pyrimidines *via* Cope-type hydroamination of 1,4-diarylbuta-1,3-diynes

Raju Singha and Jayanta K. Ray*



*Corresponding author. Tel.: +91 3222283326; fax: +91 3222282252

E-mail address: jkray@chem.iitkgp.ernet.in (J. K. Ray)

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

COMMUNICATION

Transition metal free synthesis of 2,4,6-trisubstituted pyrimidines *via* Cope-type hydroamination of 1,4-diarylbuta-1,3-diynes

Raju Singha,[a] and Jayanta K. Ray*[a]

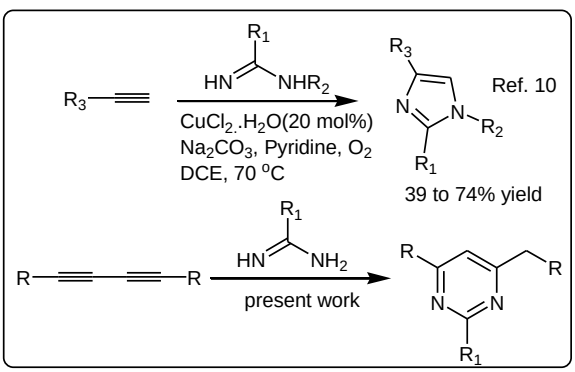
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

We have developed an efficient and transition metal free methodology for the synthesis of 2,4,6-trisubstituted pyrimidines by the Cope-type hydroamination reaction of 1,4-diarylbuta-1,3-diynes with amidines in DMSO solvent.

Pyrimidine motifs are one of the most important heterocycles, from both chemical and pharmaceutical points of view.[1] Different substituted pyrimidines are highly bio-active and have proven to display antitumor, antibacterial, antifungal, antimaleral and anticonvulsant activites.[1,2] Pyrimidine skeletones are also present in biological systems such as nucleic acids.[3] Furthermore, different conjugated pyrimidines have luminescence properties and thus, they are also used in organic light emitting devices (OLED)[4] and molecular wires.[5] Due to such great importance of pyrimidine nucleus, a number of methods have been reported in literature for their synthesis; however most of them are associated with the complex starting materials or the use of different metal catalyst.[6]

Recently a number of methods have been reported in literature for the transition metal free synthesis of important heterocycles.[7] In last decade, Beauchemin and co-workers had reported the uncatalyzed intermolecular Cope-type hydroamination reactions of alkynes/alkenes with hydrazine/hydroxylamine to form imine.[8] Later on Bao and co-workers have synthesized isooxazoles and pyrazoles using the Cope-type hydroamination reactions.[9] Recently Neuville and co-workers have synthesized 1,2,4-trisubstituted imidazoles by the reaction of terminal alkynes and amidines and in presence of copper catalyst (Scheme 1).[10]

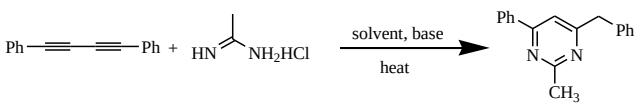


Scheme 1: Literature reports and present work

Amidines are an important class of organic compounds which can serve as a base or an ambidentate nucleophile or a bidentate nucleophile depending upon the reaction conditions.[11] Herein, we have synthesized 2,4,6-trisubstituted pyrimidines *via* catalyst free Cope-type hydroamination reaction of 1,4-diarylbuta-1,3-diynes with amidines where the amidines acts as a bidentate nucleophile.

Initially, we chose 1,4-diphenylbuta-1,3-diyne (**1a**) and acetamidine hydrochloride as model substrates to optimize the reaction conditions. Reaction of the substrates in toluene solvent and in presence of triethylamine base under refluxing condition did not give any product. Similarly DMF also failed to produce any result even at 120 °C. Then we heated the substrates in DMA solvent at 140 °C and it gave the desired product 4-benzyl-2-methyl-6-phenylpyrimidine (**2a**) in 13% yield. Under the same reaction condition, DMSO solvent produced the product **2a** in 32% yield. Thus the DMSO solvent was promoting the reaction most efficiently.[12] When the temperature was increased to150 °C, the yield of the reaction was improved to 62% within 24 hours. On further increasing the temperature to 160 °C, the yield slightly increased to 65%. Then we used different carbonate and acetate bases but they gave lower yields. All the results are shown in **Table 1**.

Table 1: Screening of the reaction conditions [a]



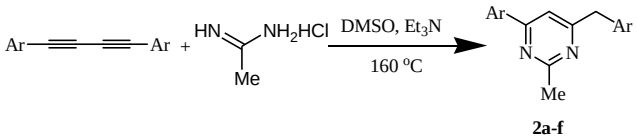
1a **2a**

Entry	Solvent	Base	Temp.(°C)	Time (h)	Yield (%)[b]
1	Toluene	Et_3N	110	48	0
2	DMF	Et_3N	120	48	0
3	DMA	Et_3N	140	48	13
4	DMSO	Et_3N	140	48	32
5	DMSO	Et_3N	150	24	62
6	DMSO	Et_3N	160	24	65
7	DMSO	NaOAc	160	24	51
8	DMSO	Na_2CO_3	160	24	43
9	DMSO	K_2CO_3	160	24	46

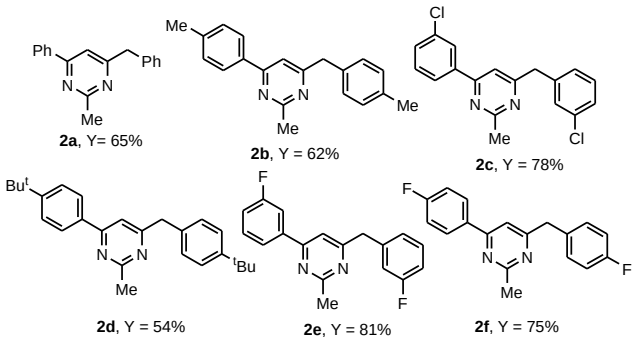
[a]Reaction conditions: 1,4-diphenylbuta1,3-diyne (0.5 mmol), acetamidinehydrochloride (3.0 equiv.), base (3.0 equiv.), solvent (5 mL). [b]Isolated yield.

From Table 1, we concluded that the optimized reaction conditions were 1,4-diphenylbuta-1,3-diyne (0.5 mmol), acetamidine hydrochloride (3 equiv), triethylamine (3 equiv.), DMSO (5 mL) and heated under air balloon at 160 °C for 24 h. Once we got the optimized reaction condition, then we applied this on different1,4-diarylbuta-1,3-diynes to examine the scope of the reaction. We have synthesized a number of 2,4,6-trisubstituted pyrimidines[13,14] and the results are shown in Table 2.

Table 2: synthesis of different 2,4,6-trisubstituted pyrimidines [a,b]

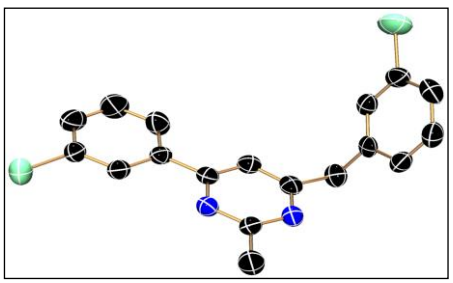


2a-f



[a] Reaction conditions: 1,4-diarylbuta-1,3-diyne (0.5 mmol), acetamidinehydrochloride (3.0 equiv.), Et_3N (3.0 equiv.), DMSO (5 mL) and heated at 160 °C for 24 h. [b] Isolated yield.

As shown in Table 2, except **2d,** the yield of the products were moderate to excellent. For the electron rich1,4-diarylbuta-1,3-diyne (Table 2, entry 2d) the yield was lower and for the electron poor 1,4- diarylbuta-1,3-diynes (Table 2, entries 2c, 2e and 2f), the yields were higher. This result implies that, the electron deficient 1,4- diarylbuta-1,3-diynes are the suitable substrates for this reaction.

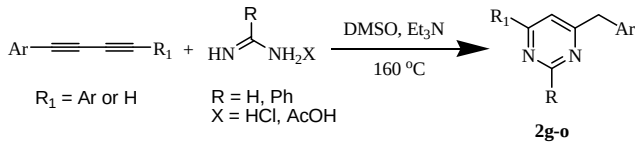


Scheme 2: The X-ray crystal structure of compound 2c

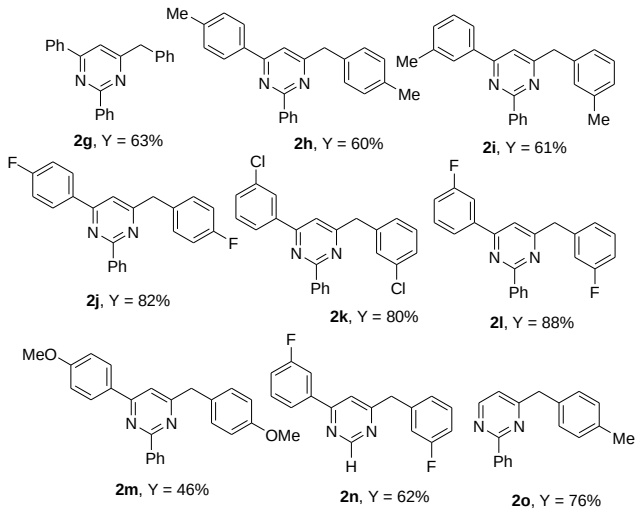
The structures of the tri-substituted pyrimidines were unambiguously confirmed from the X-ray crystal structure of the compound 2c (CCDC 990434) (Scheme 2).

After confirming the structure of the compound 2,4,6-trisubstituted pyrimidines, different 1,4-diarylbuta-1,3-diynes were subjected to reaction with benzamidinehydrochloride or formamidineacetate to test the generality of this synthetic protocol. The results are shown in Table 3.

Table 3: synthesis of different substituted pyrimidines.[a,b]



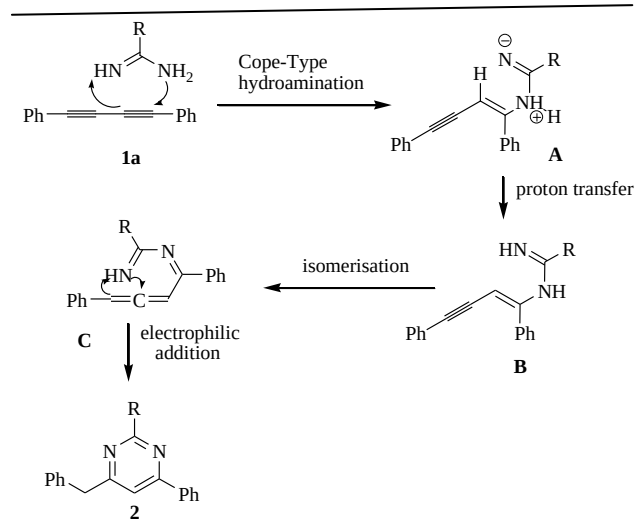
2g-o



[a] Reaction conditions: 1,3-diyne (0.5 mmol), benzamidinehydrochloride/formamidineacetate (3.0 equiv.), Et_3N (3.0 equiv.), DMSO (5 mL) and heated at 160 °C for 24 h. [b]Isolated yield.

Similarly like Table 2, the electron deficient diynes (Table 3, entries 2j, 2k and 2l) gave higher yield and the electron rich diyne (Table 3, entry 2m) gave lower yield. The yield of the reaction with formamidine acetate was quite lower (Table 3, entry 2n) and this is probably due to the decomposition of formamidine in higher temperature. The mono substituted buta-1,3-diyne (Table 3, entry 2o) gave exclusively one product in good yield. Finally the overall yield of the reaction was moderate to good. Although the reaction is good for mono or diarylbuta-1,3-diynes but the non aromatic buta-1,3-diynes are not suitable substrate for this reaction.

Scheme 3: Plausible rational for the formation of 2,4,6-trisubstituted pyrimidines.



According to our experimental results and literature reports[8,9], a plausible reaction mechanism is shown in Scheme 3. At first the amidine hydrochloride reacted with triethylamine to give free amidine. Then the intermolecular Cope-type hydroamination reaction occurred between the diyne (**1**) and amidine to give the ionic intermediate **A**, which then transformed to the intermediate **B** *via* a proton transfer process. Then the intermediate **B** converted to the intermediate **C** through the isomerisation process. Then intermediate **C** gave the final product 2,4,6-trisubstituted pyrimidines (**2**) *via* the intramolecular electrophilic addition reaction.

In conclusion, we have developed a novel and straight forward method for the synthesis of 2,4,6-trisubstituted pyrimidines using the readily available starting materials 1,4-diarylbuta-1,3-diynes and amidines. This methodology will be very much useful in organic synthesis because of its simple reaction condition, moderate to good yield, readily available starting materials and catalyst free reaction condition.

Acknowledgement:

We gratefully acknowledge DST and CSIR for providing funds and Central Research Facilities (CRF), IIT Kharagpur for the HRMS facility. R.S. thanks CSIR, New Delhi for the fellowship.

Notes and references

[a] *Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India. Tel: 91 3222283326; E-mail: jkray@chem.iitkgp.ernet.in*

† Electronic Supplementary Information (ESI) available: The detailed experimental procedures, characterisation data and the copies of ^{1}H and ^{13}C NMR spectra are available in supporting information. See DOI: 10.1039/b000000x/

1. (a) K. Undheim and T. Benneche, In comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. V. F., Eds.; Pergamon Press: London, 1996; Vol. 6, Chapter 2, pp 93-231; (b) D. J. Brown, R. F. Evans, W. B. Cowden and M. D. Fenn, Eds. In The Pyrimidines; John Wiley & Sons: New York, 2008; Vol. 52.

2. (a) A. Agarwal, K. Srivastava, S. K. Puri and M. P. S. Chauhan, *Bioorg. Med. Chem.*, 2005, **13**, 4645; (b) M. Johar, T. Manning, D. Y. Kunimoto and R. Kumar, *Bioorg. Med. Chem.*, 2005, **13**, 6663; (c) T. Sasada, F. Kobayashi, N. Sakai and T. Konakhara, *Org. Lett.*, 2009, **11**, 2161; (d) E. Gayon, M. Szymczyk, H. Gerard, E. Vrancken and J. M. Campagne, *J. Org. Chem*., 2012, **77**, 9205.

3. R. K. Murray, D. K. Granner, P. A. Mayes and V. W. Rodwell, Harper's Illustrated Biochemistry, 26th Edition, Lange Medical Books/McGraw-Hill Medical Publising Division, Section IV, Chapter-34, pp-293.

4. (a) K. T. Wong, T. S. Hung, Y. Lin, C. C. Wu, G. H. Lee, S. M. Peng, C. H. Chou and Y. O. Su, *Org. Lett*., 2002, **4**, 513; (b) K. Itami, D. Yamazaki and J. I. Yoshida, *J. Am. Chem. Soc*., 2004, **126**, 15396.

5. (a) A. Harriman and R. Ziessel, *Chem. Commun*., 1996, 1707; (b) A. Harriman and R. Ziessel, *Coord. Chem. Rev*., 1998, **171**, 331.

6. (a) P. Zhichkin, D. J. Fairfax and S. A. Eisenbein, *Synthesis*, 2002, 720; (b) A. S. Karpov and T. J. J. Muller, *Synthesis*, 2003, 2815; (c) M. Movassaghi and M. D. Hill, *J. Am. Chem. Soc*., 2006, **128**, 14254; (d) M. G. Barthakur, M. Borthakur, P. Devi, C. J. Saikia, A. Saikia, U. Bora, A. Chetia and R. C. Boruah, *Synlett*, 2007, 223; (e) O. K. Ahmad, M. D. Hill and M. Movassaghi, *J. Org. Chem*., 2009, **74**, 8460; (f) T. Sasada, F. Kobayashi, N. Sakai and T. Konakahara, *Org. Lett.*, 2009, **11**, 2161; (g) A. A. Estrada, J. P. Lyssikatos, F. S. Jean and P. Bergeron, *Synlett*, 2011, 2387; (h) E. Gayon, M. Szymczyk, H. Gérard, E. Vrancken and J.M. Campagne, *J. Org. Chem*., 2012, **77**, 9205.

7. (a) R. P. Lester and J. E. Camp, *ACS Sustainable Chem. Eng.*, 2013, **1**, 545; (b) S. Ngwerume and J. E. Camp, *J. Org. Chem*., 2010, **75**, 6271; (c) E. Y. Schmidt, I. V. Tatarinova, E. V. Ivanova, N. V. Zorina, I. A. Ushakov and B. A. Trofimov, *Org. Lett*., 2013, **15**, 104; (d) B. A. Trofimov, O. A. Shemyakina, A. G. Malkina, I. A. Ushakov, O. N. Kazheva, G. G. Alexandrov and O. A. Dyachenko, *Org. Lett*., 2010, **12**, 3200; (e) T. P. Culbertson, *J. Heterocyclic Chem*., 1979, **16**, 1423.

8. (a) P. H. Cebrowski, J. G. Roveda, J. Moran, S. I. Gorelsky and A. M. Beauchemin, *Chemm. Comm*., 2008, 492; (b) A. M. Beauchemin, J. Moran, M. E. Lebrun, C. Seguin, E. Dimitrijevic, L. Zhang and S. I. Gorelsky, *Angew. Chem. Int. Ed*., 2008, **47**, 1410.

9. (a) L. Wang, X. Yu, X. Feng and M. Bao, *Org. Lett*., 2012, **14**, 2418; (b) L. Wang, X. Yu, X. Feng and M. Bao, *J. Org. Chem*., 2013, **78**, 1693.

10. (a) J. Li and L. Neuville, *Org. Lett.*, 2013, **15**, 1752.

11. (a) J. J. Dunsford and J. E. Camp, *Tetrahedron Lett*., 2013, **54**, 4522; (b) J. R. Harjani, C. Liang and P. G. Jessop, *J. Org. Chem*., 2011, **76**, 1683; (c) C. J. Cobley, M. V. D. Heuvel, A. Abbadi and J. G. D. Vries, *Tetrahedron Lett*., 2000, **41**, 2467.

12. E. Y. Schmidt, N. V. Zorina, A. B. Zaitsev, A. I. Mikhaleva, A. M. Vasiltsov, P. Audebert, G. Clavier, R. M. Renault and R. B. Pansu, *Tetrahedron Lett*., 2004, **45**, 5489 and the references therein.

13. **General procedure for the synthesis of 2,4,6-trisubstituted pyrimidines:** The 1,4-diarylbuta-1,3-diyne (0.5 mmol), acetamidine/benzamidine hydrochloride (1.5 mmol) were taken in a round bottomed flask fitted with a condenser and then triethyl amine (1.5 mmol) and dimethyl sulfoxide (5 mL) were added. Then the reaction mixture was heated at 160 °C under air balloon for 24 h. Then the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The crude product was then purified by column chromatography using silica gel (60-120 mesh) and petroleum ether/ethylacetate (20:1) as eluent.

14. Spectral data of the representative compound 4-benzyl-2-methyl-6-phenylpyrimidine (**2a**): Yellow liquid; Yield 65%; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.81 (3H, s), 4.16 (2H, s), 7.30-7.35 (5H, m), 7.44-7.47 (4H, m), 7.94-7.99 (2H, m); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 26.3 (CH_3), 44.3 (CH_2), 113.3 (CH), 127.1 (CH), 127.5 (2 x CH), 129.0 (2 x CH), 129.1 (2 x CH), 129.5 (2 x CH), 130.9 (CH), 137.2 (C), 137.7 (C), 164.9 (C), 168.0 (C), 169.7 (C); HRMS (ESI) calculated for $C_{18}H_{17}N_2$ [M + H]$^+$: 261.1386; found: 261.1387.