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Catalyst-free synthesis of tetrahydropyrimidines via formal [3+3]-cycloaddition of imines with 1,3,5-hexahydro-1,3,5-triazines†

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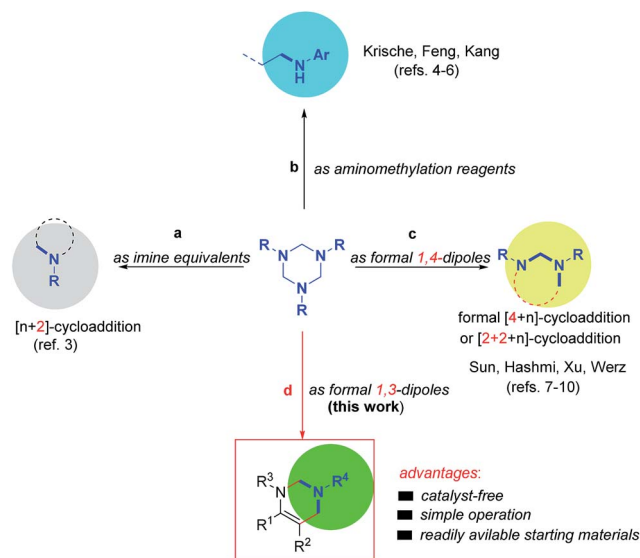
A practical and environmentally benign synthesis of poly-substituted tetrahydropyrimidines from readily available starting materials has been developed. This process features an unprecedented intermolecular formal [3+3]-annulation of imines and 1,3,5-hexahydro-1,3,5-triazines under catalyst-free conditions. Importantly, differing from previous transformations, the 1,3,5-triazines are firstly utilized as formal 1,3-dipoles in cycloaddition reactions.

Tetrahydropyrimidines are important heterocycles which have been widely explored in various biologically active molecules and advanced materials, possessing unique properties such as antiviral activity, anti-inflammatory, muscarinic agonist activity, and sensitivity to protein–DNA interactions.¹ However, efficient methods for tetrahydropyrimidine synthesis are rare² and some of them suffer from poor practicability with low yields, harsh reaction conditions and lack readily available starting materials. Therefore, to develop simple but efficient methodologies for the direct synthesis of polysubstituted tetrahydropyrimidines is highly demanded.

As stable and readily available intermediates, 1,3,5-trisubstituted-hexahydro-1,3,5-triazines (simply as 1,3,5-triazines in this text) have been previously utilized as imine equivalents in various Lewis acid promoted [n+2]-cycloaddition reactions (Scheme 1a).³ They also have been employed as precursors of *N*-aryl formaldimines in hydroaminomethylation of π -unsaturated reactants pioneered by the Krische group,⁴ and as suitable reagents in asymmetric Mannich reaction subsequently reported by the groups of Feng⁵ and Kang⁶ (Scheme 1b). Recently, inspired by Krische's work, we found that 1,3,5-triazines could be utilized as formal 1,4-dipoles in gold-catalyzed formal [4+1] and [4+3]-cycloaddition reactions to synthesize five- and seven *N*-heterocycles.^{7a} Afterwards, we have successfully developed a series of 1,3,5-triazines involved [2+2+2],^{7b} [2+1+2]^{7c,d} and formal [4+3] annulations^{7e} (Scheme 1c). Concurrently, the groups of Hashmi⁸ and Xu⁹ also described the gold-catalyzed cycloaddition of 1,3,5-triazines with activated alkynes to produce six- and seven-membered heterocycles. Just

recently, Werz and co-worker reported an elegant formal [4+3]-cycloaddition of 1,3,5-triazines with donor–acceptor cyclopropanes to prepare seven-membered ring system.¹⁰ Although the great advances, the former reports focused on the use of 1,3,5-triazines as formal 1,2- or 1,4-dipoles. In continuation with our ongoing interest, we want to report here the first use of 1,3,5-triazines as formal 1,3-dipoles to react with imines, providing tetrahydropyrimidines in moderate to excellent yields under catalyst-free reaction conditions.

Initially, the reaction of imine **1a** and 1,3,5-triazine **2a** was performed in various solvents at room temperature (Table 1). All of the solvents examined such as toluene, dichloromethane (CH₂Cl₂), chloroform (CHCl₃), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), acetonitrile (MeCN), 1,4-dioxane, methanol,



Scheme 1 Previous reports and our protocol.

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Table 1 Selected optimization^a

Entry	Solvent	Temp (°C)	Time (h)	Conv. ^b (%)	Yield ^c (%)
1	Toluene	rt	10	100	84
2	CH ₂ Cl ₂	rt	10	94	79
3	CHCl ₃	rt	10	92	78
4	DCE	rt	10	98	80
5	THF	rt	10	100	81
6	MeCN	rt	10	90	78
7	1,4-Dioxane	rt	10	93	77
8	MeOH	rt	10	92	78
9	EtOH	rt	10	87	67
10	DMF	rt	10	78	60
11	DMSO	rt	10	81	64
12	Toluene	40	7	100	84
13	Toluene	60	6	100	86
14	Toluene	80	6	100	86

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.33 mmol), solvent (6 mL).^b Determined by GC analysis. ^c Isolated yields.

ethanol, *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), were all amenable to this reaction, providing tetrahydropyrimidine **3a** in moderate to high yields with good to excellent conversion in 10 hours, whereas toluene proved to be the best one (entry 1). The reaction temperature was then evaluated. When the reaction was performed at 40 °C in toluene, shorter reaction time (7 h) and same yield (84%) were observed (entry 12). Furthermore, the reaction was finished in 6 hours at 60 °C or 80 °C and furnished **3a** in 86% yield (entries 13 and 14).

With the optimal conditions in hand, we started to examine the scope of substrates (Table 2). The reaction of 1,3,5-triazines with an array of imines was carried out at 60 °C in toluene. In the beginning, the variation of R¹ and R² groups of imines has been evaluated. For *N*-4-methoxy-substituted imines, the aryl R¹ and R² groups bearing electron-donating and electron-withdrawing groups were tolerated, providing the corresponding products (**3a–3f**) in moderate to good yields. However, longer reaction was required for the imines bearing electron-deficient aryl groups (**3c–3e**), whereas *ortho*-methyl substituted substrate gave the desired product **3f** in 61% yield. Varying R² from aryl to alkyl groups furnished **3g** (11 h) and **3h** (18 h) in 72% and 58% yields, respectively. The carboxylic ester group of R² was also amenable to the reaction, and tetrahydropyrimidine **3i** was isolated in 74% yield after 16 h. The reaction of cyclic imine with **2a** afforded **3j** in 89% yield within 8 h. The molecular structure of **3j** was characterized by X-ray diffraction.¹¹

Next, the scope of *N*-substituent of imines was examined. It was observed that *N*-aryl imines with electron-donating substituents gave the corresponding products in higher yields than the ones with electron-withdrawing groups (**3k, 3l** vs. **3m–3n**). The reaction was also applicable to *N*-alkyl imine and the

Table 2 Substrate scope^{a,b}

Variation of R^1 and R^2

3a

86%, 6 h

3b

87%, 6 h

3c

80%, 16 h

3d

64%, 18 h

3e

78%, 12 h

3f

61%, 16 h

3g

72%, 11 h

3h

58%, 18 h

3i

74%, 16 h

3j

89%, 8 h

Variation of R^3

3k

75%, 16 h

3l

68%, 18 h

3m

52%, 16 h

3n

47%, 16 h

3o

72%, 14 h

Variation of 1,3,5-triazines

3p

87%, 6 h

3q

70%, 10 h

3r

88%, 10 h

3s

77%, 12 h

3t

78%, 14 h

3u

79%, 12 h

^a Reaction conditions: all reactions were performed with **1** (0.3 mmol), **2** (0.33 mmol), in toluene (6 mL) and stirred at 60 °C for 6–18 h. ^b Isolated yields.

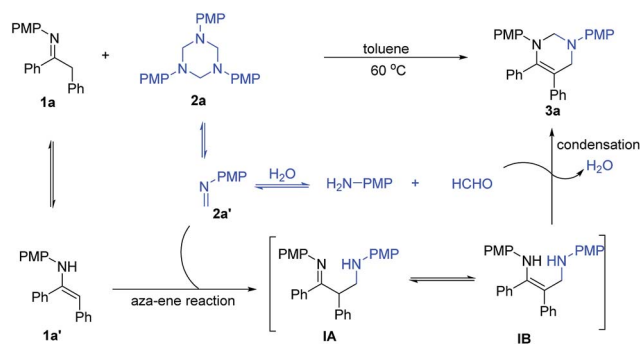
desired product **3o** was isolated in 72% yield. Finally, the scope of 1,3,5-triazines was evaluated. *N*-aryl-1,3,5-triazines bearing both electron-donating and electron-withdrawing groups were tolerated and the desired products were obtained in moderate to excellent yields (**3p** to **3t**). It should be noted that *N*-benzhydryl triazine was also tolerated, providing **3u** in 79% yield.



To examine the practicability of this protocol, a gram scale reaction was performed (Scheme 2). Treatment of 5 g of **1a** (16.6 mmol, 1 equiv.) and 1,3,5-tribenzhydryl-1,3,5-triazine (10.7 g, 18.2 mmol, 1.1 equiv.) at 60 °C in toluene for 24 h gave 6.1 g of **3u** (72% yield) as white solid after recrystallization.

Mechanistic studies were conducted to understand the reaction mechanism (Scheme 3). First, the reaction of **1a** with aniline and paraformaldehyde in toluene at 60 °C for 12 h delivered **3p**, **3a** and **4** in 42%, 19% and 9% yields, respectively, indicating the exchange of imine with aniline occurred (Scheme 3a). Next, the reaction of **1a** and **2a** in the presence of 1 equiv. of aniline provided 78% yield of **3a** and 7% yield of **3p**, providing evidence for the exchange between aniline and 1,3,5-triazine (Scheme 3b). Moreover, treatment of **1a** with **D-2a** in the presence of paraformaldehyde produces **D-3a** in 80% yield with 35% and 41% of hydrogen incorporation, indicating the decomposition of 1,3,5-triazines to formaldimines and further decomposed to aniline and formaldehyde (Scheme 3c).

Based on the above results, a possible mechanism for the catalyst-free formal [3+3]-cycloaddition is proposed in Scheme 4. The dissolution of 1,3,5-triazine **2a** in solvent would generate formaldimine **2a'**, which can further decompose to 4-methoxyaniline and formaldehyde due to the existence of small amount of water in the solvent. Imine **1a** can isomerize to enamine **1a'** in the reaction system. The whole process might be triggered by a formal aza-ene type reaction^{12,17} between enamine **1a'** and formaldimine **2a'**, generating active intermediates β -aminoimine **IA** or 1,3-diamine **IB**. These intermediates then



Scheme 4 Plausible mechanism.

react with *in situ* formed formaldehyde to generate the condensation product tetrahydropyrimidine **3a** and release one molecular of water into the reaction system. The role of water and the existence of formaldehyde can be confirmed by the crossover experiments (Scheme 3).

In summary, we have developed a novel protocol to synthesize poly-substituted tetrahydropyrimidines from readily available starting materials under catalyst-free conditions. The process is simple, practical and environmentally benign, proceeding *via* a formal [3+3]-cycloaddition between imines and 1,3,5-triazines. Typically, the 1,3,5-triazines have been firstly utilized as formal 1,3-dipoles in the cycloaddition reactions, which is unprecedented. Mechanistic studies show that this reaction is a step-wise process, namely the initial reaction of imines with *in situ* generated formaldimines, followed by condensation with formaldehyde to give the final product.

Conflicts of interest

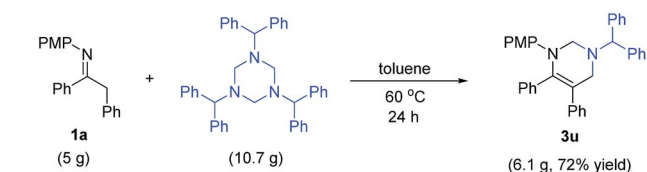
There are no conflicts to declare.

Acknowledgements

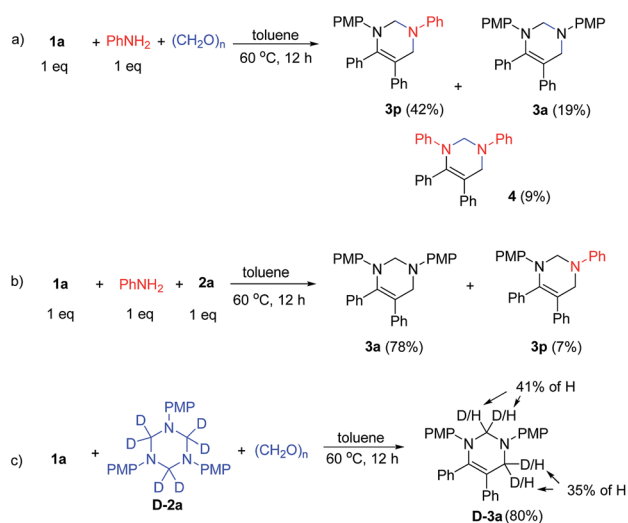
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Notes and references

- For selected examples, see: (a) S. Zhou, E. R. Kern, E. Gullen, Y.-C. Cheng, J. C. Drach, S. Matsumi, H. Mitsuya and J. Zemlicka, *J. Med. Chem.*, 2004, **47**, 6964; (b) R. Pattarini, R. J. Smeyne and J. I. Morgan, *Neuroscience*, 2007, **145**, 654; (c) C. G. Evans, S. Wisén and J. E. Gestwicki, *J. Biol. Chem.*, 2006, **281**, 33182; (d) V. Nair, G. Chi, R. Ptak and N. Neamati, *J. Med. Chem.*, 2006, **49**, 445; (e) S. Cesarini, A. Spallarossa, A. Ranise, O. Bruno, N. Arduino, M. Bertolotto, F. Dallegri, M. Tognolini, T. Gobetti and E. Barocelli, *Bioorg. Med. Chem.*, 2009, **17**, 3580; (f) S. N. Darandale, D. N. Pansare, N. A. Mulla and



Scheme 2 Large scale reaction.



Scheme 3 Mechanistic studies.



- D. B. Shinde, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2632; (g) T. B. Sundberg, Y. Liang, H. Wu, H. G. Choi, N. D. Kim, T. Sim, L. Johannessen, A. Petrone, B. Khor, D. B. Graham, I. J. Latorre, A. J. Phillips, S. L. Schreiber, J. Perez, A. F. Shamji, N. S. Gray and R. J. Xavier, *ACS Chem. Biol.*, 2016, **11**, 2105; (h) C. Carbajales, J. Azuaje, A. Oliveira, M. I. Loza, J. Brea, M. I. Cadavid, C. F. Masaguer, X. García-Mera, H. Gutiérrez-de-Terán and E. Sotelo, *J. Med. Chem.*, 2017, **60**, 3372; (i) A. Rodina, M. Vilenchik, K. Moulick, J. Aguirre, J. Kim, A. Chiang, J. Litz, C. C. Clement, Y. Kang, Y. She, N. Wu, S. Felts, P. Wipf, J. Massague, X. Jiang, J. L. Brodsky, G. W. Krystal and G. Chiosis, *Nat. Chem. Biol.*, 2007, **3**, 498; (j) B. Wei, W. Li, Z. Zhao, A. Qin, R. Hu and B. Z. Tang, *J. Am. Chem. Soc.*, 2017, **139**, 5075.
- 2 For selected examples, see: (a) B. Carboni, L. Toupet and R. Carrié, *Tetrahedron*, 1987, **43**, 2293; (b) K. Chanda, M. C. Dutta, E. Karim and J. N. Vishwakarma, *J. Heterocycl. Chem.*, 2004, **41**, 627; (c) J. D. Clark, J. T. Collins, H. P. Kleine, G. A. Weisenburger and D. K. Anderson, *Org. Process Res. Dev.*, 2004, **8**, 571; (d) K. Singh, D. Arora and J. Balzarini, *Tetrahedron*, 2010, **66**, 8175; (e) M. D. Mandler, P. M. Trugong, P. Y. Zavalij and M. P. Doyle, *Org. Lett.*, 2014, **16**, 740; (f) S. Zheng, S. Zhong, Z. Chen, W. Chen and Q. Zhu, *ACS Comb. Sci.*, 2016, **18**, 475. A highly effective multicomponent reaction was reported by Jiang and co-workers, see: (g) M. Zhang, H. Jiang, H. Liu and Q. Zhu, *Org. Lett.*, 2007, **9**, 4111; (h) H. Cao, X. Wang, H. Jiang, Q. Zhu, M. Zhang and H. Liu, *Chem.-Eur. J.*, 2008, **14**, 11623; (i) Q. Zhu, L. Huang, Z. Chen, S. Zheng, L. Lv, Z. Zhu, D. Cao, H. Jiang and S. Liu, *Chem.-Eur. J.*, 2013, **19**, 1268.
- 3 (a) H.-J. Hark, G.-S. Nam and K. P. Park, *Tetrahedron Lett.*, 1990, **31**, 1567; (b) H.-J. Ha, K.-H. Kang, J.-M. Suh and Y.-G. Ahn, *Tetrahedron Lett.*, 1996, **37**, 7069; (c) H.-J. Ha, J.-M. Suh, K.-H. Kang, Y.-G. Ahn and O. Han, *Tetrahedron*, 1998, **54**, 851; (d) H.-J. Ha, C.-J. Choi, Y.-G. Ahn, H. Yun, Y. Dong and W. K. Lee, *J. Org. Chem.*, 2000, **65**, 8384; (e) L. K. B. Garve, A. Kreft, P. G. Jones and D. B. Werz, *J. Org. Chem.*, 2017, **82**, 9235.
- 4 (a) S. Oda, B. Sam and M. J. Krische, *Angew. Chem., Int. Ed.*, 2015, **54**, 8525; (b) S. Oda, J. Franke and M. J. Krische, *Chem. Sci.*, 2016, **7**, 136.
- 5 X. Lian, L. Lin, K. Fu, B. Ma, X. Liu and X. Feng, *Chem. Sci.*, 2017, **8**, 1238.
- 6 J. Gong, S.-W. Li, S. Qurban and Q. Kang, *Eur. J. Org. Chem.*, 2017, 3584.
- 7 (a) C. Zhu, G. Xu and J. Sun, *Angew. Chem., Int. Ed.*, 2016, **55**, 11867; (b) S. Peng, S. Cao and J. Sun, *Org. Lett.*, 2017, **19**, 524; (c) P. Liu, G. Xu and J. Sun, *Org. Lett.*, 2017, **19**, 1858; (d) P. Liu, C. Zhu, G. Xu and J. Sun, *Org. Biomol. Chem.*, 2017, **15**, 7743; (e) S. Liu, P. Yang, S. Peng, C. Zhu, S. Cao and J. Sun, *Chem. Commun.*, 2017, **53**, 1152.
- 8 Z. Zeng, H. Jin, X. Song, Q. Wang, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Chem. Commun.*, 2017, **53**, 4304.
- 9 Y. Zheng, Y. Chi, M. Bao, L. Qiu and X. Xu, *J. Org. Chem.*, 2017, **82**, 2129.
- 10 L. K. B. Garve, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed.*, 2017, **56**, 9226.
- 11 CCDC 1577296 (3j).†
- 12 M. Terada, K. Machioka and K. Sorimachi, *Angew. Chem., Int. Ed.*, 2006, **45**, 2254.

