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Dimethyl Sulfoxide Serves as a Dual Synthon: Construction of 5-Methyl Pyrimidine Derivatives via Four Component Oxidative Annulation

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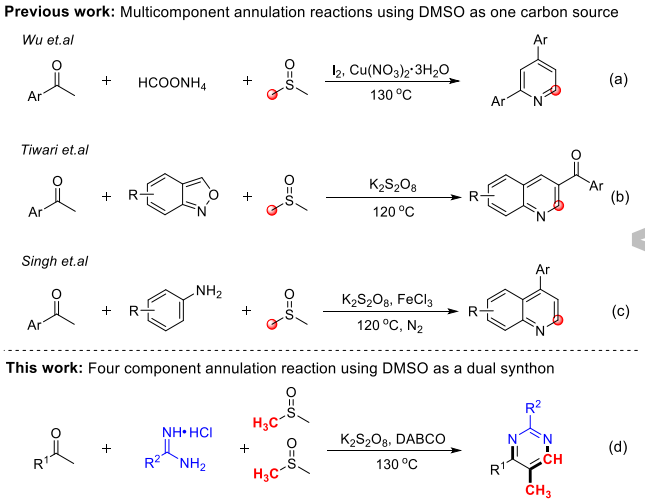
Abstract. An efficient potassium persulfate mediated four component reaction for the construction of 5-methyl pyrimidine derivatives has been established from readily available methyl ketones, amidine hydrochlorides and dimethyl sulfoxide. This transformation features dimethyl sulfoxide as a dual synthon, acting as the precursors of the methyl and methine units. Four new chemical bonds, involving two C–C and two C–N bonds were formed sequentially during the intermolecular oxidative annulation process. This synthetic method offers several advantages including broad substrate scope, good functional group tolerance and simplicity of operation.

Keywords: Activation of dimethyl sulfoxide; potassium persulfate mediated; Dual synthon; Multicomponent annulation reaction; 5-methyl pyrimidine derivatives

Dimethyl sulfoxide (DMSO) has been extensively utilized as a cheap and versatile solvent in organic synthesis.[1] Besides being an effective polar aprotic medium, activation of DMSO has become a constantly fascinating research area[2] because it can serve as a multipurpose fragment donor such as oxygen source,[3] sulfur source[4] and carbon source[5,7-10] for incorporation into target molecules. In particular, by the capture of sulfenium ion[5f,6] generated *in situ* from the activation of DMSO, examples for the rapid assembly of heterocyclic compounds have been realized.[7-10] However, in these annulation reactions, the sulfenium ion was generally intercepted by various elaborately designed substrates to proceed in an intramolecular manner,[7] illustrations for intermolecular multicomponent annulation reactions by employing DMSO as an essential building block remain rare. In 2016, our group developed an appealing $I_2/Cu(NO_3)_2{\cdot}3H_2O$-mediated reaction for the preparation of substituted pyridines by trapping the *in situ*-generated sulfenium ion (Scheme 1, a).[8] Recently, Tiwari and co-workers demonstrated a prominent intermolecular three component reaction for the construction of functionalized quinolines from readily available acetophenones and anthranils using DMSO as one carbon source (Scheme 1, b).[9] Moreover, Singh also disclosed an elegant oxidative annulation reaction to access 4-arylquinolines *via* a cascade that entails generation of a sulfenium ion, subsequent C–N and C–C bond formations, and cyclization (Scheme 1, c).[10] Despite these advancements, there is still a demand for the development of new multicomponent annulation reactions related to sulfenium ion generated from DMSO that allow efficient construction of other heterocycles. Herein, we report an unusual $K_2S_2O_8$ mediated four component reaction for the construction of 5-methyl pyrimidine derivatives (Scheme 1, d). To the best of our knowledge, this is the first example that DMSO

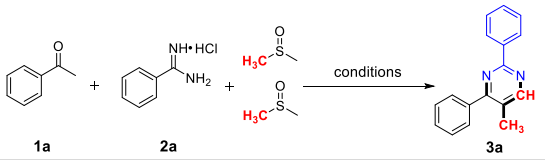


Scheme 1. Intermolecular multicomponent annulation reactions by the capture of sulfenium ion generated *in situ* from the activation of DMSO.

10.1002/adsc.201800180

serves as a dual synthon to participate in annulation reactions, acting as both precursors of the methyl and methine units. The synthetic method provides a practical and straightforward approach for the construction of diverse pyrimidine derivatives,[11] which are exemplified as privileged structural motifs that widely exist in natural products[12] and pharmaceuticals such as vitamin B1, estrogen antagonists and anticoagulant, antineuropathic pain drugs.[13]

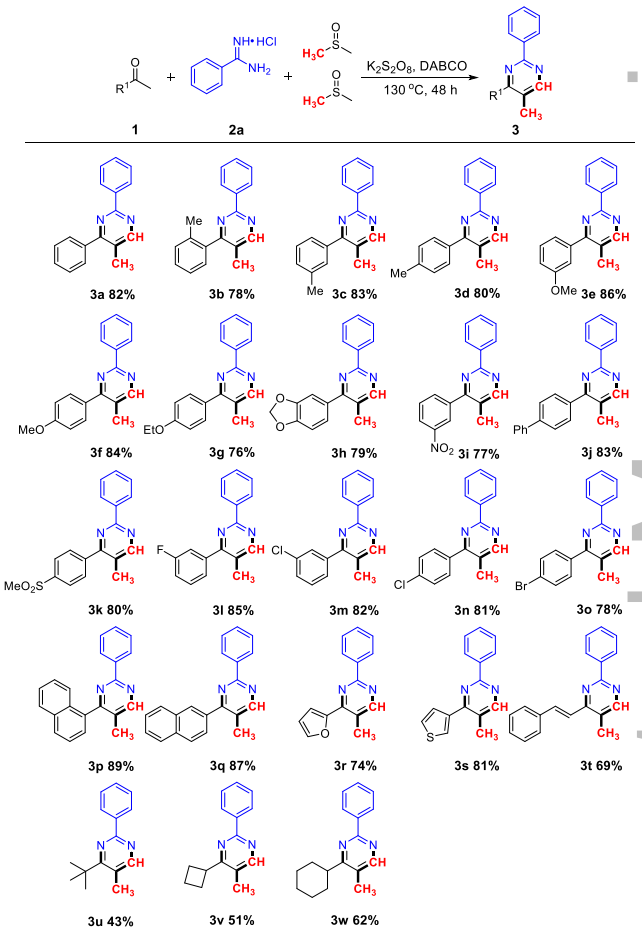
Table 1. Optimization of the Reaction Conditions[a].



entry	additive	base	temp (°C)	yield[b] (%)
1	$K_2S_2O_8$	K_2CO_3	130	58
2	$K_2S_2O_8$	Na_2CO_3	130	59
3	$K_2S_2O_8$	Cs_2CO_3	130	62
4	$K_2S_2O_8$	$NaHCO_3$	130	32
5	$K_2S_2O_8$	NaOAc	130	30
6	$K_2S_2O_8$	K_3PO_4	130	61
7	$K_2S_2O_8$	K_2HPO_4	130	73
8	$K_2S_2O_8$	DBU	130	42
9	**$K_2S_2O_8$**	**DABCO**	**130**	**82**
10	$K_2S_2O_8$	Pyridine	130	16
11	$K_2S_2O_8$	Piperdine	130	75
12	$K_2S_2O_8$	Et_3N	130	43
13	$K_2S_2O_8$	t-BuOK	130	12
14	-	DABCO	130	n.r
15	$Na_2S_2O_8$	DABCO	130	76
16	$(NH_4)_2S_2O_8$	DABCO	130	45
17	TBHP	DABCO	130	trace
18	H_2O_2	DABCO	130	48
19	$K_2S_2O_8$	DABCO	120	72
20	$K_2S_2O_8$	DABCO	110	46
21[c]	$K_2S_2O_8$	DABCO	130	75
22[d]	$K_2S_2O_8$	DABCO	130	54

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), additive (1.0 mmol), base (0.8 mmol) were heated in 3 mL DMSO for 48 h. [b] Isolated yields. [c] $K_2S_2O_8$ (0.8 mmol, 2.0 equiv). [d] **2a** (0.6 mmol, 1.5 equiv).

During our study of the oxidative cross-coupling of aryl methyl ketones and benzamidine hydrochlorides,[14] an unexpected product 5-methyl-2,4-diphenylpyrimidine (**3a**) was isolated in 58% yield when the reaction was performed in the presence of 2.5 equiv of $K_2S_2O_8$ and 2.0 equiv of K_2CO_3 at 130 °C in DMSO for 48 h (Table 1, entry 1). Encouraged by this initial and promising result, various reaction parameters were systematically evaluated, including additives, bases and temperature (Table 1). A range of inorganic and organic bases were first screened (Table 1, entries 2–13), and DABCO was found to provide the optimum product yield. The additive also proved to be essential for this transformation. Without the addition of $K_2S_2O_8$, the reaction did not proceed to give the desired product **3a** (Table 1, entry 14). Other selected oxidants, such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, TBHP and H_2O_2 were examined subsequently (Table 1, entries 15–18), but none of these had a positive impact on the outcome of the reaction. Changes to the temperature gradient were also investigated, but no improvement in the yield of **3a** was obtained (Table 1, entries 19–20). Additional optimization tests revealed that a decrease in the amount of $K_2S_2O_8$ or **2a** would lead to lower yields (Table1, entry 21–22). Eventually, the optimized reaction conditions were determined as **1a** (0.4 mmol) with **2a** (0.8 mmol) in the presence of $K_2S_2O_8$ (1.0 mmol) and DABCO (0.8 mmol) in 3mL DMSO at 130 °C for 48 h.



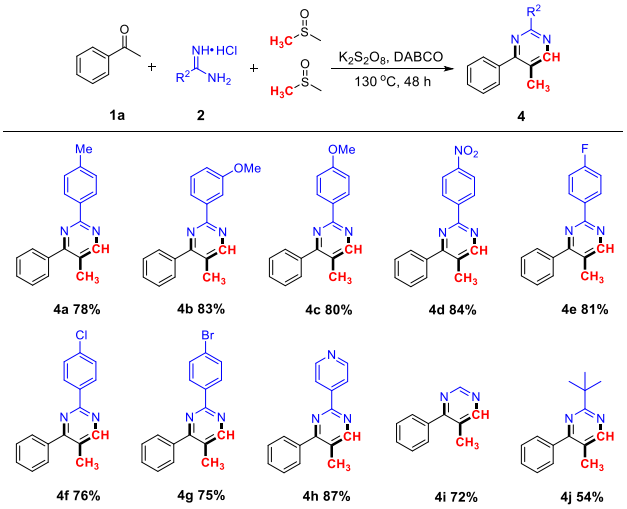
Scheme 2. Scope of Methyl Ketones. Reaction conditions: **1** (0.4 mmol), **2a** (0.8 mmol), $K_2S_2O_8$ (1.0 mmol) and DABCO (0.8 mmol) in DMSO (3 mL) at 130 °C for 48 h Isolated yields.

Having identified the optimized reaction conditions, we further evaluated the substrate generality of this four-component oxidative annulation reaction by testing methyl ketones substrates (Scheme 2). A variety of aryl methyl ketones bearing both electronically neutral (4-H, 2-Me, 3-Me, 4-Me), electron-donating (3-OMe, 4-OMe, 4-OEt, 3,4-OCH_2O) and electron-withdrawing (3-NO_2, 4-Ph, 4-SO_2Me) substituents all reacted smoothly to deliver the corresponding products in good to excellent yields

10.1002/adsc.201800180

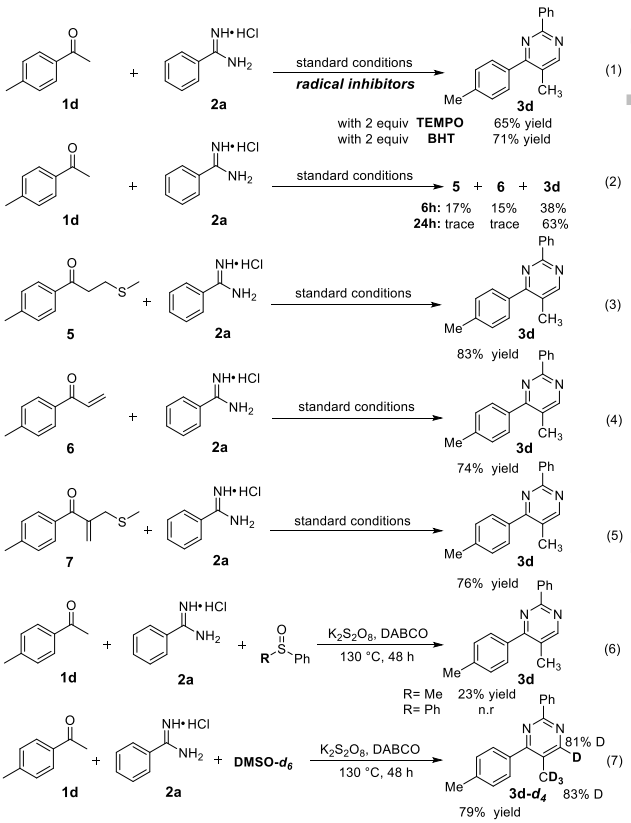
(76–86%; **3a–3k**). Halogenated substituents (3-F, 3-Cl, 4-Cl, 4-Br) were also found to be compatible with the reaction (78–85%; **3l–3o**), which provided opportunities for further synthetic elaboration. Moreover, the sterically hindered (1-naphthyl and 2-naphthyl) methyl ketones also furnished the expected products in excellent yields (87–89%; **3p–3q**). This method was further applied to several representative heteroaryl methyl ketones such as 1-(furan-2-yl)ethan-1-one, 1-(thiophen-3-yl)ethan-1-one and α,β-unsaturated methyl ketone, to our satisfaction, the optimized conditions proved to be suitable for the conversion to these structurally novel molecules (69–81%; **3r–3t**). Additionally, aliphatic methyl ketones, such as 3,3-dimethylbutan-2-one, 1-cyclobutylethan-1-one and 1-cyclohexylethan-1-one were also tolerated well, delivering the desired products in moderate yields (43–62%; **3u–3w**).

In order to obtain a diverse library of polyfunctional pyrimidines, the scope of the reaction was subsequently expanded to various amidine hydrochlorides (Scheme 3). Noteworthy, the electronic properties of the substituents on the aromatic ring system were shown to have little influence on the effciency of this reaction. Benzamidine hydrochlorides with electronically neutral (4-Me), electron-donating (3-OMe, 4-OMe), electron-withdrawing (4-NO_2) and halogen-substituted (4-F, 4-Cl, 4-Br) groups attached to the aryl ring all proceeded smoothly to give their corresponding products in good to excellent yields (75–84%; **4a–4g**). In addition, the heteroaryl substrate pyridine-4-carboximidamide and aliphatic substrates such as formimidamide and pivalimidamide were also found to readily undergo the transformation, thus producing the target products in satisfactory yields (54–87%; **4h–4j**). Furthermore, the structures of **3i** and **4f** were unambiguously determined by X-ray crystallographic analysis[15] (see the Supporting Information).



Scheme 3. Scope of Amidine Hydrochlorides. Reaction conditions: **1a** (0.4 mmol), **2** (0.8 mmol), $K_2S_2O_8$ (1.0 mmol) and DABCO (0.8 mmol) in DMSO (3 mL) at 130 °C for 48 h. Isolated yields.

With the scope of the method established, we then turned our attention to evaluate the reaction mechanism (Scheme 4). Initially, the reaction was performed in the presence of different radical inhibitors (2.0 equiv of TEMPO or BHT), which still gave the desired product **3d** in 65% and 71% yields, indicating that a radical process might not involved in this transformation. When the reaction of 1-(p-tolyl)ethan-1-one **1d** and benzamidine hydrochloride **2a** under standard conditions was terminated at 6 h, product **3d** was obtained in 38% yield and was accompanied by the generation of 3-(methylthio)-1-(p-tolyl)propan-1-one (**5**) and 1-(p-tolyl)prop-2-en-1-one (**6**) in 17% and 15% yields, respectively. Upon prolonging the reaction to 24 h, **5** and **6** disappeared, whereas the yield of **3d** increased to 63%. In the following experiments, these possible intermediates **5** and **6** were isolated to react independently with benzamidine hydrochloride **2a** under the optimized conditions, and both were successfully transformed to the desired product **3d** in good yields. These results further confirmed that **5** and **6** might be key intermediates in the reaction sequence. Additionally, presynthesized 2-((methylthio)methyl)-1-(p-tolyl)prop-2-en-1-one (**7**) together with **2a** heated in DMSO also furnished **3d** in 76% yield, indicating that **7** might be a candidate intermediate.

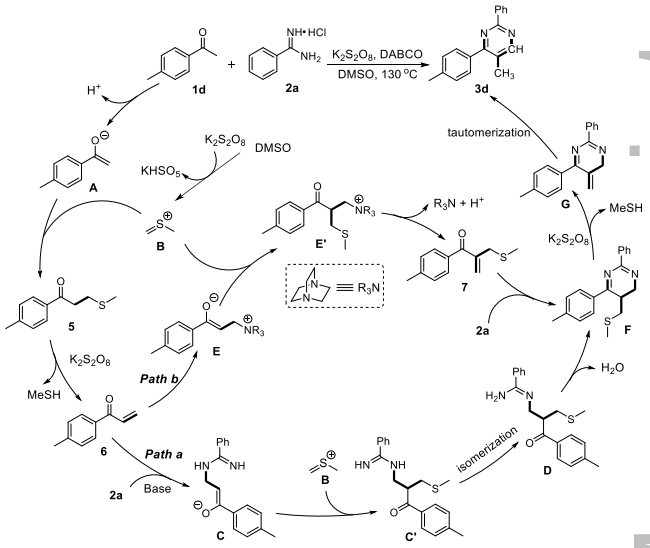


Scheme 4. Control Experiments.

Several additional experiments were performed to further probe the role of DMSO in this transformation. The reaction of **1d** and **2a** was subsequently carried out using methyl phenyl sulfoxide as the solvent to deliver product **3d** in 23% yield, whereas no reaction occurred when diphenyl sulfoxide was used instead. Moreover, the deuterium-labeling experiment of **1d** and **2a** in DMSO-d_6 was conducted under standard conditions to produce **3d**-d_4 in 79% yield with 83% deuteration at the methyl unit and 81% deuteration at the methine unit of the pyrimidine framework. These two control experiments revealed that DMSO was an essential component as well as the solvent. Two molecules of DMSO served as the source of the methyl unit and the methine unit to participate in this multicomponent intermolecular oxidative annulation reaction.

In accordance with our experimental observations and related literature reports,[2,5a,5f,16] a possible mechanism for this four component oxidative annulation reaction was proposed by using 1-(p-tolyl)ethan-1-one (**1d**) and benzamidine hydrochloride (**2a**) as an example (Scheme 5). Initially, DMSO was activated by $K_2S_2O_8$ to generate the sulfenium ion **B** *in situ*, which was immediately captured by enolate **A** derived from **1d** to give 3-(methylthio)-1-(p-tolyl)propan-1-one (**5**). In the presence of $K_2S_2O_8$, **5** further underwent elimination of MeSH to produce α, β-unsaturated ketone **6**. Subsequently, the base-promoted intermolecular aza-Michael addition of benzamidine hydrochloride (**2a**) with **6** proceeded to give intermediate **C**. Next, **C** was transformed into the annulated intermediate **F** *via* consecutive electrophilic addition with another equivalent of **B** and subsequent intermolecular condensation. Finally, after the demethylthioation of **F** followed by tautomerization of the double bonds, the desired product **3d** was obtained. It is noticeable that although we did not detected the possible intermediate **7** during the whole reaction process, in view of earlier publications where methyl ketones could couple with DMSO to produce β-methylthio isopropenylketones,[16] an alternative reaction pathway cannot be overlooked. As shown in path **b**, intermediate **6** could undergo 1,4-addition with nucleophilic organic base DABCO to form intermediate **E**. The electrophilic addition of **E** with sulfenium ion **B** followed by elimination of ammonium leaded to the formation of intermediate **7**. The annulation reaction of **7** with **2a** then occurred to give intermediate **F**, which was finally converted to the desired product **3d** *via* sequential demethylthioation and tautomerization as expected.

In summary, we have developed an efficient $K_2S_2O_8$ mediated four component intermolecular oxidative annulation reaction for the direct synthesis of 5-methyl pyrimidine derivatives. Readily available methyl ketones, amidine hydrochlorides and DMSO can be assembled in a one-pot manner by the sequential formation of two C–C and two C–N bonds. Notably, this method represents a novel strategy for capturing the *in situ*-generated sulfenium ion by the activation of DMSO, and isotope-labeling experiments revealed that DMSO served as the source of the methyl and methine units. Further studies to develop new multicomponent annulation reactions by using DMSO as a multiple fragments donor for efficient assembly of other heterocycles are currently underway in our laboratory.



Scheme 5. Proposed Mechanism.

Experimental Section

A mixture of acetophenone **1a** (0.4 mmol), benzamidine hydrochloride **2a** (0.8 mmol), $K_2S_2O_8$ (1.0 mmol), DABCO (0.8 mmol) and DMSO (3.0 mL) were added to a pressure vessel, then stirred at 130 °C for 48 h. after disappearance of the reactant (monitored by TLC), then added 50 mL water to the mixture, extracted with EtOAc 3 times (3 × 50 mL). The extract was washed with 30% NaCl solution (V/V), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether / EtOAc = 20/1) to afford the desired products **3a** as a white solid.

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References

[1] a) D. Martin, A. Weise, H. J. Niclas, *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 318; b) I. Soroko, Y. Bhole, A. G. Livingston, *Green Chem.* **2011**, *13*, 162; c) W. M. Nelson, *Green solvents forchemistry: Perspectives and practice in Green Chemistry*, Oxford University Press, USA, 1st edn., **2003**, ch. 3, pp 60–62 and ch. 5, pp. 116–132.

[2] For recent reviews, see: a) X. -F. Wu, K. Natte, *Adv. Synth. Catal.* **2016**, *358*, 336; b) E. Jones-Mensah, M. Karki, J. Magolan, *Synthesis* **2016**, *48*, 1421 and references therein.

[3] For selected examples, see: a) S. Song, X. Huang, Y. -F. Liang, C. Tang, X. Li, N. Jiao, *Green Chem.* **2015**, *17*, 2727; b) Y. -F. Liang, X. Li, X. Wang, M. Zou, C. Tang, Y. Liang, S. Song, N. Jiao, *J. Am. Chem. Soc.* **2016**, *138*, 12271; c) Y. Ashikari, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2011**, *133*, 11840; d) R. Xu, J. -P. Wan, H. Mao, Y. Pan, *J. Am. Chem. Soc.* **2010**, *132*, 15531; e) Y. -F. Liang, K. Wu, S. Song, X. Li, X. Huang, N. Jiao, *Org. Lett.* **2015**, *17*, 876; f) R. Chebolu, A. Bahuguna, R. Sharma, V. K. Mishra, P. C. Ravikumar, *Chem. Commun.* **2015**, *51*, 15438; g) Q. Gao, X. Wu, S. Liu, A. Wu, *Org. Lett.* **2014**, *16*, 1732.

[4] For selected examples, see: a) F. Luo, C. Pan, L. Li, F. Chen, J. Cheng, *Chem. Commun.* **2011**, *47*, 5304; b) P. Sharma, S. Rohilla, N. Jain, *J. Org. Chem.* **2015**, *80*, 4116; c) X. Gao, X. Pan, J. Gao, H. Jiang, G. Yuan, Y. Li, *Org. Lett.* **2015**, *17*, 1038; d) F. -L. Liu, J. -R. Chen, Y. -Q. Zou, Q. Wei, W.-J. Xiao, *Org. Lett.* **2014**, *16*, 3768; e) Y. Jiang, T. -P. Loh, *Chem. Sci.* **2014**, *5*, 4939; f) M. M. D. Pramanik, N. Rastogi, *Chem. Commun.* **2016**, *52*, 8557; g) T. Shen, X. Huang, Y. -F. Liang, N. Jiao, *Org. Lett.* **2015**, *17*, 6186; h) T. Jia, A. Bellomo, K. E. Baina, S. D. Dreher, P. J. Walsh, *J. Am. Chem. Soc.* **2013**, *135*, 3740.

[5] For selected examples, see: a) Y. -F. Liu, P. -Y. Ji, J. -W. Xu, Y. -Q. Hu, Q. Liu, W. -P. Luo, C. -C. Guo, *J. Org. Chem.* **2017**, *82*, 7159; b) J. Qian, Z. Zhang, Q. Liu, T. Liu, G. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 3119; c) X. Ren, J. Chen, F. Chen, J. Cheng, *Chem. Commun.* **2011**, *47*, 6725; d) R. Pothikumar, C. Sujatha, K. Namitharan, *ACS Catal.* **2017**, *7*, 7783; e) O. P. S. Patel, D. Anand, R. K. Maurya, P. P. Yadav, *J. Org. Chem.* **2016**, *81*, 7626; f) X. Jiang, C. Wang, Y. Wei, D. Xue, Z. Liu, J. Xiao, *Chem. -Eur. J.* **2014**, *20*, 58.

[6] a) R. Pummerer, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282; b) A. Padwa, S. K. Bur, D. M. Danca, J. D. Ginn, S. M. Lynch, *Synlett* **2002**, 851.

[7] For selected examples, see: a) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu, Q. Zhang, *Chem. Commun.* **2013**, *49*, 6439; b) J. Yuan, J. -T. Yu, Y. Jiang, J. Cheng, *Org. Biomol. Chem.* **2017**, *15*, 1334; c) C. Xie, Z. Zhang, D. Li, J. Gong, X. Han, X. Liu, C. Ma, *J. Org. Chem.* **2017**, *82*, 3491; d) H. Wang, S. Sun, J. Cheng, *Tetrahedron Lett.* **2017**, *58*, 3875.

[8] X. Wu, J. Zhang, S. Liu, Q. Gao, A. Wu, *Adv. Synth. Catal.* **2016**, *358*, 218.

[9] S. B. Wakade, D. K. Tiwari, P. S. K. P. Ganesh, M. Phanindrudu, P. R. Likhar, D. K. Tiwari, *Org. Lett.* **2017**, *19*, 4948.

[10] S. D. Jadhav, A. Singh, *Org. Lett.* **2017**, *19*, 5673.

[11] For reviews on pyrimidine synthesis, see: a) M. Mahfoudh, R. Abderrahim, E. Leclerc, J. -M. Campagne, *Eur. J. Org. Chem.* **2017**, 2856; b) M. D. Hill, M. Movassaghi, *Chem. Eur. J.* **2008**, *14*, 6836; c) M. Radi, S. Schenone, M. Botta, *Org. Biomol. Chem.* **2009**, *7*, 2841.

[12] a) I. M. Lagoja, *Chem. Biodiversity* **2005**, *2*, 1; b) T. K. Bradshaw, D. W. Hutchinson, *Chem. Soc. Rev.* **1977**, *6*, 43.

[13] a) S. Manzetti, J. Zhang, D. vander Spoel, *Biochemistry* **2014**, *53*, 821; b) A. A. Parent, J. R. Gunther, J. A. Katzenellenbogen, *J. Med. Chem.* **2008**, *51*, 6512; c) W. Tu, J. Fan, H. Zhang, G. Xu, Z. Liu, J. Qu, F. Yang, L. Zhang, T. Luan, J. Yuan, A. Gong, J. Feng, P. Sun, Q. Dong, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 141; d) Y. Lan, Y. Chen, X. Cao, J. Zhang, J. Wang, X. Xu, Y. Qiu, T. Zhang, X. Liu, B. F. Liu, G. Zhang, *J. Med. Chem.* **2014**, *57*, 10404.

[14] X. Wu, Q. Gao, S. Liu, A. Wu, *Org. Lett.* **2014**, *16*, 2888.

[15] CCDC 1817236 and CCDC 1817237 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[16] a) Y. Liu, X. Zhan, P. Ji, J. Xu, Q. Liu, W. Luo, T Chen, C. Guo, *Chem. Commun.* **2017**, *53*, 5346. b) Z. -K. Wen, X. -H. Liu, Y. -F. Liu, J. -B. Chao, *Org. Lett.* **2017**, *19*, 5798.

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UPDATE

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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