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Palladium-Catalyzed 3-Aryl-5-acyl-1,2,4-thiadiazoles Formation from Ketones, Amidines and Sulfur Powder

Zilong Wang,[a] Hao Xie,[a] Fuhong Xiao,[a] Yanjun Guo,[a] Huawen Huang*[a] and Guo-Jun Deng*[a][b]

Abstract: An efficient strategy for 3,5-disubstituted-1,2,4-thiadiazoles from ketones, amidines and sulfur powder under palladium-catalyzed conditions has been developed. Aromatic ketones acted as carbon source and acyl source in this transformation. This reaction provided an efficient approach for 3-aryl-5-acyl-1,2,4-thiadiazoles from readily available starting materials.

Introduction

Thiadiazole is prevalent and important five-membered heterocyclic motif containing a sulfur atom and two nitrogen atoms. The thiadiazole system constitutes the key structures of many natural products, functional materials as well as pharmaceutical drugs.[1] As an isomer of thiadiazole, the 1,2,4-thiadiazole scaffold which has an unsymmetrical five-membered ring also showed a broad range of biological activities, including anti-inflammatory, antifungal activity, antibiotic activity, anticonvulsant and intense muscarinic activity (Figure 1).[2] The cefozopran, which contains a 3,5-disubstituted 1,2,4-thiadiazole motif, is a commercial drug with antibacterial activity.[3] Despite their wide applications in pharmacology, only few methods have been developed for the preparation of this kind of five-membered heterocycles.[4] The classic method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles relys on the oxidative dimerization reaction of thioamides.[5] A large number of oxidant such as hydrogen peroxide,[5a] nitrous acid,[5b] thionyl chloride,[5c] HCl-DMSO,[5d] pyridinium salt-DMSO,[5e] bis(acyloxyiodo)arenes,[5f] N,N'-dibromo phenytoin,[5g] 2,4,6-trichloro-1,3,5-triazine,[5h] and polymer-supported iodobenzene diacetate[5i] have been successfully used for the conversion of thioamides and thiobenzamides to the corresponding 1,2,4-thiadiazoles with substituents at positions 3 and 5. Few other methods have also been developed for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles using other starting materials such as aryl nitriles,[6] 3,5-dichloro-1,2,4-thiadiazole,[7] amidines,[8] and isothocyanates.[9] Direct functionalization of 3,5-dihalo-1,2,4-thiadiazoles could provide an alternative approach for preparation of other 3,5-disubstituted 1,2,4-thiadiazoles via palladium-catalyzed Suzuki-Miyaura process.[10]

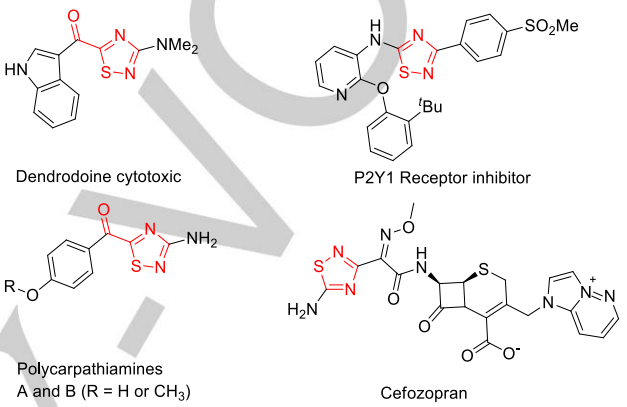
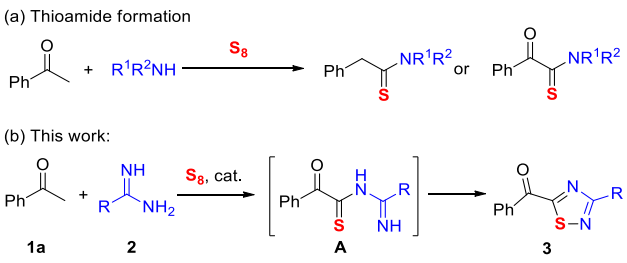


Figure 1. Representative 3,5-disubstituted-1,2,4-thiadiazoles in natural products and potencial pharmaceutical drugs.

Above all, most of the mentioned methods for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles require strong oxidative conditions or highly functionalized starting materials. Thus it would be highly desirable to develop synthetically diverse methodology for 1,2,4-thiadiazoles from simple starting materials As well known, thioamides or α-ketothioamides could be readily formed through the three-component coupling of methyl ketone, amine, and elemental sulfur under facile reaction conditions, i.e. Willgerodte Kindler reaction (Scheme 1a).[11] We reasoned in such a system using amidines, a variant of amines instead, would form the thioamide intermediate **A**, which undergo an oxidative N-S bond formation[12] to afford 5-acyl-1,2,4-thiadiazoles (Scheme 1b). Acyl substituent at the C5 position is of great value since the alkaloids polycarpathiamines, isolated from the ascidina *Polycarpa aurata* (Figure 1),[13] showed significant cytotoxic activity agaist L5178Y murine lymphoma, while efficient method for the preparation of 5-acyl substituted 1,2,4-thiadiazoles is still rare.[14] As our continuing efforts using



Scheme 1. Strategy for 1,2,4-thiadiazole formation inspired by the synthesis of thioamides.

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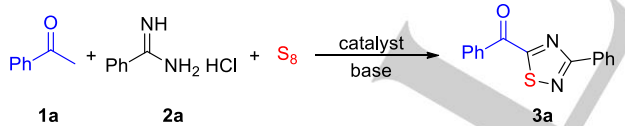
cheap and readily available elemental sulfur as the sulfur source to construct sulfur-containing heterocycles,[15] herein, we report a facile annulation for the 3-aryl-5-acyl-1,2,4-thiadiazole synthesis from amidines, acetophenones and sulfur powder[16] under palladium-catalyzed reaction conditions. The methyl group *ortho* to the carbonyl position of acetophenones acted as one carbon source in this transformation.

Results and Discussion

Based on our previously demonstrated thiadiazole formation from 2-methylquinolines, amidines and elemental sulfur,[17] we started the investigation of the reaction of acetophenone (**1a**), benzamidine (**2a**) and elemental sulfur in a base system under argon atmosphere at 160 °C (Table 1). No desired product was observed when the reaction was carried out in the absence of transition metal catalyst using K_2HPO_4 as base and DMSO as solvent (entry 1). Addition of palladium catalyst could significantly improve the reaction yield and the desired product phenyl(3-phenyl-1,2,4-thiadiazol-5-yl)methanone (**3a**) was observed in 49% yield when $Pd(OAc)_2$ was employed (entry 2). Among the various palladium catalysts investigated, $PdCl_2$ showed the best efficiency to give the desired product in 74% yield (entry 5). A brief base screening showed that stronger base is not suitable to convert the starting materials to the corresponding product (entries 6-10). Several organic solvents and H_2O were screened and all of them are not good reaction media for this kind of reaction (entries 11-15). A control reaction showed that much poor yield was obtained when the reaction was carried out in the absence of base (entry 16). Moderate yield could still be obtained when the reaction was carried out under air (entry 17). Decreasing the reaction temperature resulted in a relatively low yield (entry 18). Finally, only 38% yield was observed when employing 1 equivalent of sulfur, which indicated the elemental sulfur served as not only a reactant but as an oxidant in this reaction system.

Table 1. Optimization of the reaction conditions.[a]



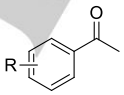
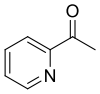
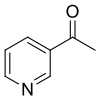
1a **2a** **3a**

Entry	Catalyst	Base	Solvent	Yield (%)[b]
1		K_2HPO_4	DMSO	0
2	$Pd(OAc)_2$	K_2HPO_4	DMSO	49
3	$PdBr_2$	K_2HPO_4	DMSO	67
4	$Pd(OH)_2$	K_2HPO_4	DMSO	51
5	$PdCl_2$	K_2HPO_4	DMSO	74
6	$PdCl_2$	K_3PO_4	DMSO	51
7	$PdCl_2$	$K_4P_2O_7$	DMSO	56
8	$PdCl_2$	KOH	DMSO	7
9	$PdCl_2$	K_2CO_3	DMSO	48
10	$PdCl_2$	$KHCO_3$	DMSO	14
11	$PdCl_2$	K_2HPO_4	PhOMe	trace
12	$PdCl_2$	K_2HPO_4	PhCl	trace
13	$PdCl_2$	K_2HPO_4	DMF	trace
14	$PdCl_2$	K_2HPO_4	Toluene	trace
15	$PdCl_2$	K_2HPO_4	H_2O	trace
16	$PdCl_2$		DMSO	24
17[c]	$PdCl_2$	K_2HPO_4	DMSO	59
18[d]	$PdCl_2$	K_2HPO_4	DMSO	56
19[e]	$PdCl_2$	K_2HPO_4	DMSO	38

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), S (1.0 mmol), catalyst (10 mol%), base (1.0 mmol), solvent (0.6 mL) at 130 °C under argon for 24 h. [b] Isolated yield based on **1a**. [c] Under air. [d] At 100 °C. [e] S (0.2 mmol) was used.

Table 2. Reaction of **2a** with various aromatic ketones.[a]

1 **2a** **3**

Entry	Ketone		Product	Yield (%)[b]
				
1	R = 4-H	**1a**	**3a**	74
2	R = 4-CH_3	**1b**	**3b**	73
3	R = 4-OMe	**1c**	**3c**	68
4	R = 4-*iso*-butyl	**1d**	**3d**	80
5	R = 4-CN	**1e**	**3e**	48
6	R = 4-Ph	**1f**	**3f**	70
7	R = 3-OMe	**1g**	**3g**	78
8	R = 2,4-dimethyl	**1h**	**3h**	61
9	R = 3,4-dimethoxy	**1i**	**3i**	65
10		**1j**	**3j**	50
11		**1k**	**3k**	35
12		**1l**	**3l**	43
13		**1m**	**3m**	51

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), S (1.0 mmol), catalyst (10 mol%), base (1.0 mmol), solvent (0.6 mL) at 130 °C under argon for 24 h. [b] Isolated yield based on **1a**. [c] Under air. [d] At 100 °C. [e] S (0.2 mmol) was used.

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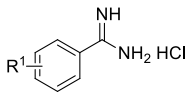
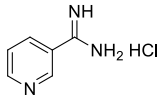
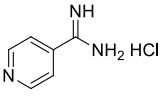
With the optimized conditions in hand, a variety of acetophenones were examined under the optimized reaction conditions, as summarized in Table 2. Similar yields were obtained when electron-donating groups presented at the *para* position (entries 2-4). The desired product **3d** was achieved in 80% when an *iso*-butyl substituent was employed (entry 4). The reaction yield significantly decreased when a strong electron-withdrawing substituent was presented (entry 5). Acetophenone with a phenyl group at the *para* position (**1f**) also reacted smoothly with **2a** and elemental sulfur to provide the corresponding product **3f** in 70% yield (entry 6). The steric effect of the substituent slightly affected the reaction yield; when 1-(3-methoxyphenyl)ethanone (**1g**) was used, the product **3g** was obtained in 78% yields (entry 7). Acetophenones with two electron-donating methyl functionalities (**1h** and **1j**) were also suitable substrates to give the desired products in good yields (entries 8 and 9). To our delight, hetero aromatic ketones bearing thiophen-2-yl, furan-2-yl, and pyridine-2-yl functionalities worked well under the optimized reaction conditions to provide the corresponding 1,2,4-thiadiazoles in moderate yields (entries 10-13).

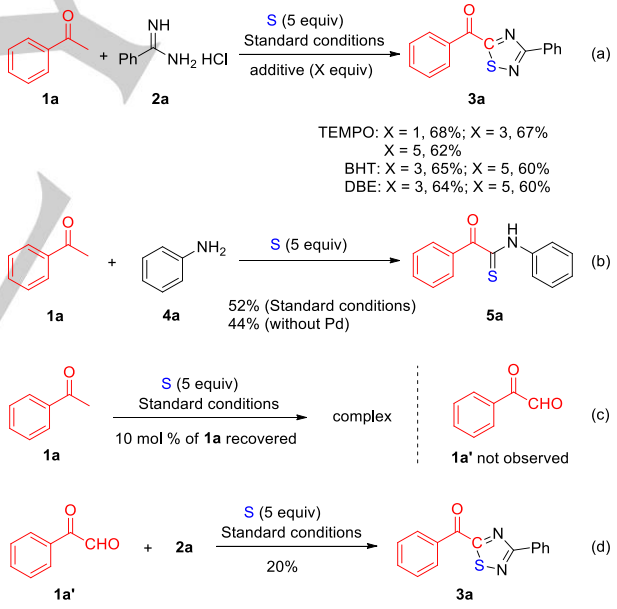
Table 3. Reaction of **1a** with various amidines.[a]

Entry	Amidine		Product	Yield [%][b]
				
1	R^1 = 4-CH_3	**2b**	**3n**	60
2	R^1 = 4-CF_3	**2c**	**3o**	75
3	R^1 = 4-NO_2	**2d**	**3p**	42
4	R^1 = 4-Br	**2e**	**3q**	52
5	R^1 = 2-CH_3	**2f**	**3r**	65
6	R^1 = 2-Cl	**2g**	**3s**	72
7		**2h**	**3t**	51
8		**2i**	**3u**	65

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), S (1.0 mmol), catalyst (10 mol%), base (1.0 mmol), solvent (0.6 mL) at 130 °C under argon for 24 h. [b] Isolated yield based on **1a**. [c] Under air. [d] At 100 °C. [e] S (0.2 mmol) was used.

After screening various acetophenones for this kind of reaction, we next investigated various amidine hydrochlorides to further explore the reaction scope and limitations (Table 3). Several substituents at the para position of benzamidine were investigated under the given conditions and good yields were obtained when methyl and trifluoromethyl substituents were employed (entries 1 and 2). However, the reaction is less efficient when a strong electron-withdrawing nitro group was presented (entry 3). When a bromo group presented at the para position, the desired product **3q** was obtained in 52% yield (entry 4). The effect of substituent position was also investigated and similar reaction yields were obtained when methyl and chloro groups were presented at the *ortho* position (entries 5 and 6). Notably, pyridyl amidines were well tolerated in this reaction system, providing **3t** and **3u** in moderate to good yields (entries 7 and 8).

To understand the mechanism of the reaction, we performed a number of control experiments (Scheme 1). First, the addition of 2,2,4,4-tetramethyl-1-piperidinyloxy (TEMPO), butylated hydroxytoluene (BHT), or ethene-1,1-diyldibenzene (DBE) to the reaction system did not inhibit the reaction (Scheme 2a), suggesting the reaction may not proceed through a radical pathway. Second, the coupling of acetophenone **1a** with aniline **4a** and elemental sulfur occurred well to afford thioamide **5a** under the standard reaction conditions or in the absence of palladium catalyst (Scheme 2b). Thereby the transition metal catalyst probably played a role not in the thioamide formation but in the step of N-S bond formation, in which both reductive elimination and electrophilic amination pathway were possibly involved. Then we found that only 10 mol % of acetophenone were recovered when the reaction was carried out in the absence of **2a** (Scheme 2c), which means the interaction of **1a** and sulfur may be the initial step. And 2-oxo-2-phenylacetaldehyde (**1a'**) was not observed in this reaction, although the desired product **3a** was obtained in 20% yield when **1a'** was subjected to the standard reaction conditions, (Scheme 2d).



Scheme 2. Control experiments.

Conclusions

In summary, we have developed a novel approach for 3,5-disubstituted-1,2,4-thiadiazoles from amidines, acetophenones and elemental sulfur under palladium-catalyzed reaction conditions. Cheap and readily available sulfur powder was acted as the sulfur source to react with amidine and methyl group *ortho* to the carbonyl group. All of the 21 products are new compounds and this method affords an efficient approach for the

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rapid synthesis of 3-aryl-5-acyl-1,2,4-thiadiazoles from readily available starting materials.

Experimental Section

General procedure for 3-aryl-5-acyl-1,2,4-thiadiazole synthesis. A 10 mL oven-dried reaction vessel was charged with acetophenone (**1a**, 24 μL, 0.2 mmol) benzimidamide hydrochloride (**2a**, 47 mg, 0.3 mmol), sulfur powder (32 mg, 1.0 mmol), potassium hydrogen phosphate anhydrous (173 mg, 1 mmol), palladium chloride (3.6 mg, 10 mol %), and DMSO (0.6 mL) under argon. The reaction vessel was stirred at 130 °C for 24 h. After cooling to room temperature, the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 30:1) to give 39.4 mg **3a** as light yellow solid, yield 74%, mp 87-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67- 8.60 (m, 2H), 8.42- 8.36 (m, 2H), 7.76-7.71 (m, 1H), 7.61 (m, 2H), 7.56-7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 183.0, 174.4, 134.7, 134.1, 132.3, 131.2, 130.8, 128.8, 128.7, 128.3; HRMS calcd. for $C_{15}H_{10}N_2OS$ $[M+H]^+$ 267.0587, found 267.0587.

Acknowledgements

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Keywords: palladium • thiadiazoles • ketones • sulfur • amidines

[1] a) Y. Li, J. Geng, Y. Liu, S. Yu, G. Zhao, *ChemMedChem* **2013**, *8*, 27; b) D. Kumar, N. M. Kumar, K. H. Chang, K. Shah, *Eur. J. Med. Chem.* **2010**, *45*, 4664; c) A. I. Rosenbaum, C. C. Cosner, C. J. Mariani, F. R. Maxfield, O. Wiest, P. Helquist, *J. Med. Chem.* **2010**, *53*, 5281; d) S. K. De, J. L. Stebbins, L. H. Chen, M. Riel-Mehan, T. Machleidt, R. Dahl, H. Yuan, A. Emdadi, E. Barile, V. Chen, R. Murphy, M. Pellecchia, *J. Med. Chem.* **2009**, *52*, 1943; e) Y. Hu, C. Y. Li, X. M. Wang, Y. H. Yang, H. L. Zhu, *Chem. Rev*. **2014**, *114*, 5572.

[2] a) A. Castro, T. Castano, A. Encinas, W. Porcal, C. Gil, *Bioorg. Med. Chem.* **2006**, *14*, 1644; b) F. Kurzer, *Adv. Heterocycl. Chem.* **1982**, *32*, 285; c) A. M. Popov, V. L. Novikov, O. S. Radchenko, G. B. Elyakov, *Dokl. Biochem. Biophys*. **2002**, *385*, 213; d) M. Wessels, G. M. König, A. D. Wright, *J. Nat. Prod.* **2001**, *64*, 1556; e) H. Kang, W. Fenical, *Tetrahedron Lett*. **1996**, *37*, 2369.

[3] Y. Izawa, K. Okonogi, R. Hayashi, T. Iwahi, T. Yamazaki, A. Imada, *Antimicrob. Agents Chemother*. **1993**, *37*, 100.

[4] D. J. Wilkins, P. A. Bradley, *Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds., Pergamon, New York, 1996, Vol. 4, Chapter 10, pp 307-354.

[5] a) J. R. Cashman, R. P. Hanzlik, *J. Org. Chem.* **1982**, *47*, 4645; b) M. W. Cronyn, T. W. Nakagawa, *J. Am. Chem. Soc.* **1952**, *74*, 3693; c) A. Castro, T. Castano, A. Encinas, W. Porcal, C. Gil, *Bioorg. Med. Chem.* **2006**, *14*, 1644; d) U. Miotti, *J. Chem. Soc. Perkin Trans.* **1991**, *2*, 617; e) Y. Takikawa, K. Shimada, K. Sato, S. Sato, *Bulll. Chem. Soc. Jpn.* **1985**, *58*, 995; f) E. A. Mamaeva, A. A. Bakibaev, *Tetrahedron* **2003**, *59*, 7521; g) H. Z. Boeini, *Synth. Commun.* **2011**, *41*, 2932; h) A. R. Khosropour, J. Noei, *Monatsh. Chem.* **2010**, *141*, 649; i) D. P. Cheng, Z. C. Chen, *Synth. Commun.* **2002**, *14*, 2155; j) A. S. Mayhoub, E. Kiselev, M. Cushman, *Tetrahedron Lett*. **2011**, *52*, 4941; k) L. Ze, M Khaliq, Z. Zhou, C. B. Post, R. J. Kuhn, M. Cushman, *J. Med. Chem*. **2008**, *51*, 4660; l) A. D. Shutalev, E. A. Kishko, S. G. Alekseeva, *Chem. Heterocyclic Compd*. **1997**, *33*, 352; m) A. S. Gurjar, V.,risano, A. D. Simone, V. S. Velingkar, *Bioorg. Chem*. **2014**, *57*, 90.

[6] J. Noei, A. R. Khosropour, *Tetrahedron Lett.* **2013**, *54*, 9.

[7] A. A. Farahat, D. W. Boykin, *Heterocycles* **2012**, *85*, 2437.

[8] Y. J. Wu, Y. Zhang, *Tetrahedron Lett*. **2008**, *49*, 2869.

[9] a) D. Martin, H. Graubaum, S. Kulpe, *J. Org. Chem*. **1985**, *50*, 1295; b) Y. Dürüst, M. Yildirim, A. Aycan, *J. Chem. Res*. **2008**, 235; c) H. Y. Kim, S. H. Kwak, C. H. Lee, Y. D. Gong, *Tetrahedron* **2014**, *70*, 8737.

[10] a) P. M. Wehn, P. E. Harrington, J. E. Eksterowicz, *Org. Lett*. **2009**, *11*, 5666; b) A. A. Farahat, D. W. Boykin, *Heterocycles* **2012**, *85*, 2437.

[11] a) D. L. Priebbenow, C. Bolm, *Chem. Soc. Rev.* **2013**, *42*, 7870; b) E. V. Brown, *Synthesis* **1975**, 358; c) M. Nooshabadi, K. Aghapoor, H. Reza Darabi, M. Majid Mojtahedi, *Tetrahedron Lett.* **1999**, *40*, 7549; d) K. Okamoto, T. Yamamoto, T. Kanbara, *Synlett* **2007**, 2687; e) O. I. Zbruyev, N. Stiasni, C. O. Kappe, *J. Comb. Chem.* **2003**, *5*, 145; f) J. E. Valdez-Rojas, H. Ríos-Guerra, A. L. Ramírez-Sánchez, G. García-González, C. Álvarez-Toledano, J. G. López-Cortés, R. A. Toscano, J. G. Penieres-Carrillo, *Can. J. Chem.* **2012**, *90*, 567; g) H.-Z. Li, W.-J. Xue, A.-X. Wu. *Tetrahedron* **2014**, *70*, 4645.

[12] a) Z. Wang, Y. Kuninobu, M. Kanai, *J. Org. Chem.* **2013**, *78*, 7337; b) A. Mariappan, K. Rajaguru, N. M. Chola, S. Muthusubramanian, N. Bhuvanesh, *J. Org. Chem.* **2016**, *81*, 6573; c) H.-Y. Kim, S. H. Kwak, G.-H. Lee, Y.-D. Gong, *Tetrahedron* **2014**, *70*, 8737; d) W. Fan, Q. Li, Y Li, H. Sun, B. Jiang, G. Li, *Org. Lett.* **2016**, 18, 1258; e) C. Lee, X. Wang, H.-Y. Jang, *Org. Lett.* **2015**, *17*, 1130; f) F.-J. Chen, G. Liao, X. Li, J. Wu, B.-F. Shi, *Org. Lett.* **2014**, *16*, 5644; g) Z. Zhou, Y. Liu, J. Chen, E. Yao, J. Cheng, *Org. Lett.* **2016**, *18*, 5268; h) J. Chen, Y. Jiang J.-T. Yu, J. Cheng, *J. Org. Chem.* **2016**, *81*, 271.

[13] a) C. D. Pham, H. Weber, R. Hartmann, V. Wray, W. H. Lin, D. W. Lai, P. Proksch, *Org. Lett*. **2013**, *15*, 2230; b) W. Wang, T. Oda, A. Fujita, R. E. P. Mangindaan, T. Nakazawa, K. Ukai, H. Kobayashi, M. Namikoshi, *Tetrahedron* **2007**, *63*, 409; c) N. Lindquist, W. Fenical, *Tetrahedron Lett*. **1990**, *31*, 2389.

[14] a) J. Cho, K. Kim, *J. Heterocyclic Chem*. **1992**, *29*, 1473; b) G. L'abbe, P. Vossen, W. Dehaen, L. Meervelt, *Bulletin des Societes Chimiques Belges* **1996**, *105*, 335; c) K. Kim, J. Cho, S. Yoon, *J. Chem. Soc. Perkin Trans. 1* **1995**, 253.

[15] a) Y. Liao, Y. Peng, H. Qi, G.-J. Deng, H. Gong, C.-J. Li, *Chem. Commun.* **2015**, *51*, 1031; b) J. Chen, G. Li, Y. Xie, Y. Liao, F. Xiao, G.-J. Deng, *Org. Lett.* **2015**, *17*, 5870.

[16] For a selected review on transformation of sulfur powder into complicated sulfur-containing chemicals, see: H. Liu, X. F. Jiang, *Chem. Asian J*. **2013**, *8*, 2546.

[17] H. Xie, J. H. Cai, Z. L. Wang, H. Huang, G.-J. Deng, *Org. Lett*. **2016**, *18*, 2196.

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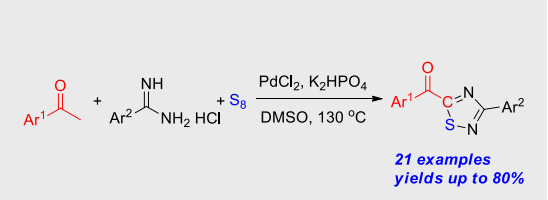

Palladium-catalyzed 1,2,4-thiadiazole formation from readily available ketones, amidines and sulfur powder has been developed.

*methodology

Cyclization

Zilong Wang, Hao Xie, Fuhong Xiao, Yanjun Guo, Huawen Huang, Guo-Jun Deng**

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Palladium-Catalyzed 3-Aryl-5-acyl-1,2,4-Thiadiazoles Formation from Ketones, Amidines and Sulfur Powder

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