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Quick construction of a C–N bond from arylsulfonyl hydrazides and C_{sp2}–X compounds promoted by DMAP at room temperature†

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An efficient approach for C–N bond construction by the coupling reaction of arylsulfonyl hydrazides and C_{sp2}–X compounds is described for the first time with good yields at room temperature. The reaction promoted by the simple base DMAP displays excellent regioselectivity as well as high functional group tolerance with 41 examples. Even for inactive C_{sp2}–Cl compounds, the metal-free transformation also affords a satisfactory yield after prolonging the reaction time, which is comparable to that of the corresponding C_{sp2}–Br compound. The good effect of DMAP and its action mechanism are confirmed by the competitive experiments of reactivity between Cl-substituted and Br-substituted substrates and the single-crystal X-ray analysis of the key intermediate quaternary ammonium salt. Importantly, the application of this method for a gram-scale (even over 10 g) preparation can be accomplished.

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Introduction

Due to good stability and reactivity, readily available arylsulfonyl hydrazides have attracted considerable attention and been widely used in the synthesis of various natural products and bioactive molecules.^{1,2} Particularly, arylsulfonyl hydrazides have usually been employed as arylation,³ sulfonylation⁴ or thioetherification⁵ agents to construct C–C or C–S bonds for the synthesis of aromatic hydrocarbons, sulfones and thioethers in recent years.

For the reaction between arylsulfonyl hydrazides and halides, sulfonyl hydrazides are generally used to react with C_{sp3}–X (I, Br, Cl) compounds in the presence of a strong base such as sodium hydride to form *N*-substituted sulfonyl

hydrazides^{1,6} (Scheme 1a). However, there are only a few studies on the reaction between sulfonyl hydrazides and less active C_{sp2}–X compounds. The limited number of reports mainly concentrate on the formation of a C–S bond by the copper-catalyzed arylthiolation (Scheme 1b)⁷ and sulfonylation reaction (Scheme 1c).⁸

To our knowledge, the reaction of building C–N bond between C_{sp2}–X compounds and sulfonyl hydrazides to form *N*-substituted sulfonyl hydrazides has not been reported yet in the previous researches. Herein, we reported a metal-free catalytic reaction between sulfonyl hydrazides and non-aromatic C_{sp2}–X (X = Br, Cl) compounds, 3,4-dihalo-2(5*H*)-furanones, in the presence of readily available organic base DMAP at room temperature (Scheme 1, this work).

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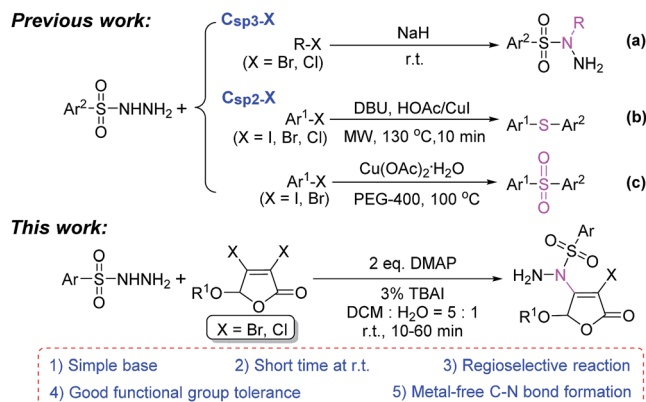
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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and ¹H, ¹³C spectra for all compounds and data of single-crystal X-ray analysis. CCDC 1885760 and 1885761. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra03403j



Scheme 1 The reaction of arylsulfonyl hydrazides with halides.



Results and discussion

Optimization of reaction conditions

For the first time, we provide a new approach for C–N bond construction by the coupling reaction of C_{sp^2} -X compounds and sulfonyl hydrazides. More importantly, this approach is also adapted to the less active C_{sp^2} -Cl compounds, which can afford comparable yield to C_{sp^2} -Br compounds. Moreover, the 2(5H)-furanone moiety is frequently found in natural products⁹ and drug molecules,^{10,11} which makes the synthesis of 2(5H)-furanone compounds with polyfunctional groups pharmaceutically valuable. Thus, we choose 3,4-dihalo-2(5H)-furanones as non-aromatic C_{sp^2} -X (X = Br, Cl) reactants in this investigation.

Initially, the condition parameters were optimized by selecting the reaction of 3,4-dibromo-5-methoxy-2(5H)-furanone **1a** and *p*-toluene sulfonylhydrazide **2a** as the model reaction. As shown in Table 1, the reaction does not occur in the absence of catalyst (Entry 1). While using copper salt (CuI), 1,10-phenanthroline (Phen) and sodium carbonate (Na_2CO_3) as the catalytic system (Entry 2), the reaction still does not occur. Further changing the base to potassium fluoride (KF), the target product **3a** can be obtained with 30% yield (Entry 3). Even without the addition of CuI and Phen, **3a** can also be obtained with 32% yield (Entry 4). Thus, we did not use CuI and Phen any more in the following screening. Controlling the other conditions,

different organic bases were also investigated (Entries 4–7). Obviously, using 4-dimethylaminopyridine (DMAP) gives the best yield of **3a**, which is up to 53% (Entry 5).

The optimization of solvents was further carried out (Table 1, Entries 8–12). The results indicate that dichloromethane (DCM) is found to be the best in single solvent system and the yield of **3a** can be 78% (Entry 11). We also discussed the effect of mixed solvent system. In DCM–H₂O with a volume ratio of 5 : 1, the yield of **3a** is decreased to 62% (Entry 13). However, after the addition of 3% tetrabutylammonium iodide (TBAI) as a phase transfer catalyst, the yield of **3a** is markedly increased to 82% (Entry 14). Compared with other organic solvent and water with a volume ratio of 5 : 1 as the mixed solvent (Entries 14–16), the yield of **3a** in DCM–H₂O is the best (Entry 14). However, with the increase of water fraction in this mixed solvent, the yield of **3a** is decreased to 70% (Entry 17).

It can be learnt from Entries 14 and 18–20 in Table 1 that the amount of base also plays an important role in this reaction system. The optimized dosage of DMAP is 2.0 eq. (Entry 14). In addition, the feed ratio of reactants was discussed and the results were collected in Entries 14 and 21–22. It can be found that when the feed ratio of **1a** and **2a** is 1 : 1.2, the yield of **3a** is the highest value of 82% (Entry 14). Altering the reaction temperature and time, no better changes can be achieved as monitored by TLC. Thus, the optimized reaction conditions

Table 1 Optimization of reaction conditions^a

Entry	Cat. (or additive) (eq.)	1a : 2a	Solvent	Yield ^b (%)
1	—	1 : 1.2	DMF	Trace
2	CuI (0.1) Phen (0.1) Na_2CO_3 (2.0)	1 : 1.2	DMF	Trace
3	CuI (0.1) Phen (0.1) KF (2.0)	1 : 1.2	DMF	30
4	KF (2.0)	1 : 1.2	DMF	32
5	DMAP (2.0)	1 : 1.2	DMF	53
6	DABCO (2.0)	1 : 1.2	DMF	49
7	DBU (2.0)	1 : 1.2	DMF	38
8	DMAP (2.0)	1 : 1.2	EtOH	45
9	DMAP (2.0)	1 : 1.2	MeCN	65
10	DMAP (2.0)	1 : 1.2	THF	52
11	DMAP (2.0)	1 : 1.2	DCM	78
12	DMAP (2.0)	1 : 1.2	Toluene	37
13	DMAP (2.0)	1 : 1.2	DCM : H ₂ O = 5 : 1	62
14	DMAP (2.0), TBAI (0.03)	1 : 1.2	DCM : H₂O = 5 : 1	82
15	DMAP (2.0), TBAI (0.03)	1 : 1.2	DCE : H ₂ O = 5 : 1	76
16	DMAP (2.0), TBAI (0.03)	1 : 1.2	Toluene : H ₂ O = 5 : 1	66
17	DMAP (2.0), TBAI (0.03)	1 : 1.2	DCM : H ₂ O = 1 : 1	70
18	DMAP (1.0), TBAI (0.03)	1 : 1.2	DCM : H ₂ O = 5 : 1	58
19	DMAP (1.5), TBAI (0.03)	1 : 1.2	DCM : H ₂ O = 5 : 1	69
20	DMAP (2.5), TBAI (0.03)	1 : 1.2	DCM : H ₂ O = 5 : 1	78
21	DMAP (2.0), TBAI (0.03)	1 : 1	DCM : H ₂ O = 5 : 1	75
22	DMAP (2.0), TBAI (0.03)	1.2 : 1	DCM : H ₂ O = 5 : 1	79

^a Reaction conditions: all reactions were performed with **1a** (0.5 mmol), **2a** (0.6 mmol) and solvent (3 mL), at room temperature (r.t.), 30 min.

^b Isolated yield.



were identified as 2.0 eq. DMAP, 3 mol% of TBAI, **1a** : **2a** = 1 : 1.2, a mixture of DCM and H₂O (v : v = 5 : 1) as the solvent at room temperature for 30 min.

Scope of reaction substrates

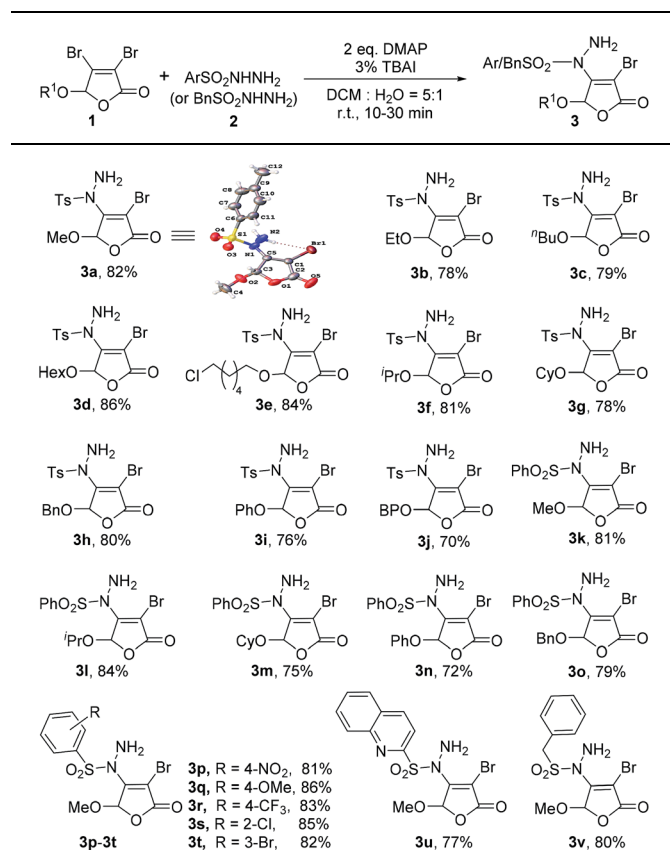
Under the optimized reaction conditions, we further studied the scope of the reaction substrate with respect to 5-substituted 3,4-dibromo-2(5*H*)-furanones and sulfonyl hydrazides, respectively. The results are summarized in Table 2. Interestingly, all reactions of 5-substituted 3,4-dibromo-2(5*H*)-furanones **1** and *p*-toluene sulfonylhydrazide (**2a**) occur in high yields (70–86%, **3a–3j**). Especially, the substituted 2(5*H*)-furanones with 5-alkoxy, such as methoxy, ethoxy, *n*-butoxy, *n*-hexyloxy (HexO), isopropoxy, cyclohexyloxy (CyO), can give the products in good yields (78–86%, **3a–3g**). For example, 82% of **3a** (methoxy) was isolated, while **3f** (isopropoxy) is obtained in 81% yield. Even for the larger CyO, the product **3g** was also successfully obtained and the yield is as high as 78%. Thus, the steric hindrance effect of 5-substituted group on the yield is not particularly obvious.

Noteworthy, the catalytic process is highly chemoselective in a case where 2(5*H*)-furanone contains more than one potentially reactive group. For example, for the substrate of **6**-

chlorohexyloxy, the sulfonyl hydrazide is highly selective to react with C_{sp2}-Br at the C-4 of 2(5*H*)-furanone to form **3e**, instead of reacting with C_{sp3}-Cl at the 5-substituted group. Moreover, when 5-substituted group is benzyloxy (BnO), the yield of **3h** can also reach to 80% as expected. For the substituted 2(5*H*)-furanones with aryloxy, *e.g.*, phenoxy, biphenyloxy (BPO), the relatively lower yields are obtained (70–76%, **3i–3j**). Further, a series of 5-substituted 3,4-dibromo-2(5*H*)-furanones as substrates **1** were explored in the reaction with phenylsulfonyl hydrazide (**2b**). The reaction also has good tolerance on different functional groups (*e.g.*, alkoxy, aryloxy) in good yields (72–84%, **3l–3o**).

In addition, many arylsulfonyl hydrazides **2** with electron-donating (*e.g.*, methoxy) or electron-withdrawing (*e.g.*, halogen, nitro, trifluoromethyl) groups can react with 3,4-dibromo-5-methoxy-2(5*H*)-furanone **1a** to produce the corresponding products **3p–3t** in good yields (81–86%). As anticipated, heteroaryl sulfonyl hydrazide is also suitable in the protocol with satisfactory result (**3u**). Importantly, benzyl sulfonyl hydrazide, as a kind of alkyl-based sulfonyl hydrazides can be successfully applied (**3v**). All the obtained products **3a–3v** have been characterized by ¹H and ¹³C NMR spectroscopic measurements including the single crystal X-ray structure of **3a**,¹² which can be seen in ESI† for details.

Table 2 Substrate scope of various 5-substituted 3,4-dibromo-2(5*H*)-furanones **1** and sulfonyl hydrazides **2**^{a,b}



^a Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), DMAP (1.0 mmol), DCM (2.5 mL), H₂O (0.5 mL) and TBAI (0.015 mmol) were added and stirred at room temperature until complete consumption of **1**, which was monitored by TLC. ^b Isolated yield.

Reactivity of 3,4-dichloro-2(5*H*)-furanones

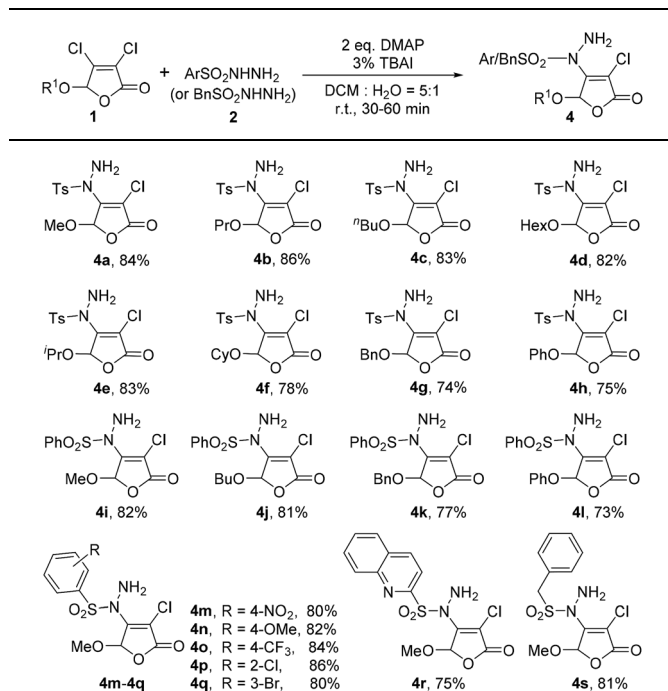
On the basis of above investigation on 3,4-dibromo-2(5*H*)-furanones, we further studied the reactivity of the lower active 3,4-dichloro-2(5*H*)-furanones with arylsulfonyl hydrazides. To our delight, good productivity for these 3,4-dichloro-2(5*H*)-furanones can also be gained by prolonging reaction time to 30–60 minutes, as shown in Table 3.

The experimental results reveal that the gratifying yields can be obtained from both substrates bearing alkoxy and aryloxy moieties as 5-substituted group. For the methoxy, propoxy, *n*-butoxy, HexO, isopropoxy, CyO, the yield is from 78% to 86% (**4a–4f**); for BnO (**4g**) and phenoxy (**4h**), the yields are 74% and 75%, respectively. Similarly, 5-substituted 3,4-dichloro-2(5*H*)-furanones can also be reacted with phenylsulfonyl hydrazide (**2b**) in yield of 73% to 82% (**4i–4l**). Especially, when arylsulfonyl hydrazides **2** containing different functional groups, such as alkoxy, halogen, nitro and CF₃, are utilized to react with 3,4-dichloro-5-methoxy-2(5*H*)-furanone **1**, the corresponding products can be acquired with satisfactory yields (**4m–4q**). It is worth noting that quinoline-2-sulfonylhydrazide and benzyl sulfonyl hydrazide are also suitable reaction partners for this novel transformation (**4r–4s**).

Generally, the activity of the chlorinated substrates is lower than that of the brominated substrates.^{11a,11c} However, the above results indicate that, comparing with 3,4-dibromo-2(5*H*)-furanones, the yields given by 3,4-dichloro-2(5*H*)-furanones are not reduced. The serial competitive experiments show that though 3,4-dibromo-2(5*H*)-furanones have higher activity and faster reaction rate to complete the reaction in a shorter time, the comparable yields can be obtained from the 3,4-dichloro-2(5*H*)-furanones after prolonging reaction time once the amount of



Table 3 Substrate scope of various 5-substituted 3,4-dichloro-2(5*H*)-furanones **1** and sulfonyl hydrazides **2**^{a,b}

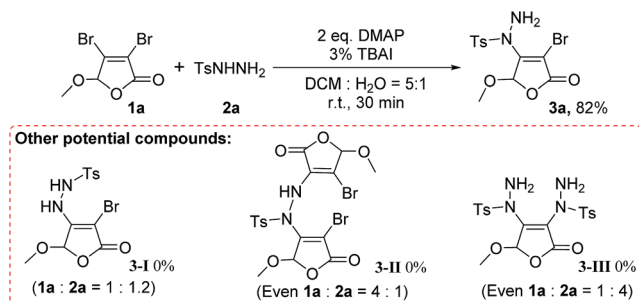


^a Reaction conditions: **1** (0.50 mmol), **2** (0.60 mmol), DMAP (1.0 mmol), DCM (2.5 mL), H₂O (0.5 mL) and TBAI (0.015 mmol) were added and stirred at room temperature until complete consumption of **1**, which was monitored by TLC. ^b Isolated yield.

sulfonyl hydrazide is enough also (see ESI† for details). These indicate that the activity of DMAP is so high that it is very easy for DMAP to form intermediate with 3,4-dihalo-2(5*H*)-furanones (which is involved in the reaction mechanism, and will be discussed in the following). Hence, the reactivity of both 3,4-dibromo-2(5*H*)-furanones and the 3,4-dichloro-2(5*H*)-furanones can give close reaction yields.

Regioselectivity of reaction

The protocol shows excellent regioselectivity in the reaction. As shown in Scheme 2, we did not find the primary nitrogen substituted product **3-I**. Even increased the ratio of **1a** : **2a** to 4 : 1, neither **3-I** nor *N,N'*-disubstituted product **3-II** was detected. This means the primary nitrogen in arylsulfonyl hydrazide



Scheme 2 Regioselectivity of reaction.

does not participate in the reaction under our conditions. At the same time, the product **3-III** cannot be observed under the standard conditions (even **1a** : **2a** = 1 : 4). It indicates that the bromine at the C-3 position of 3,4-dibromo-2(5*H*)-furanone **1a** is less active and does not participate in the reaction yet. Therefore, for both kinds of reactants, 3,4-dihalo-2(5*H*)-furanones and arylsulfonyl hydrazides, this transformation is highly regioselective.

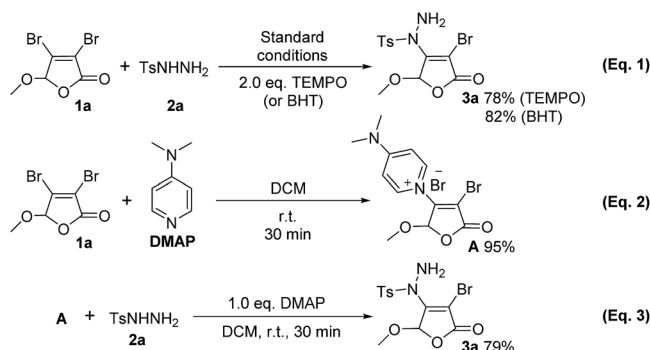
Plausible reaction mechanism

In order to gain more insight into our reaction mechanism, two control experiments were performed using 2.0 eq. radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) under the standard conditions (Scheme 3, eqn (1)). It can be found that the desired product **3a** is still obtained in 78% and 82% yields, respectively. These observations demonstrate that a radical process should be excluded in this transformation.

Organocatalysis plays an increasingly significant role in organic synthesis recently.¹³ DMAP has been widely used in organic reaction as catalyst^{14,15} or base.¹⁶ During our experiments, quaternary ammonium salt **A** was surprisingly found (its chemical structure was confirmed by X-ray,¹² see ESI† for details). Furthermore, stirring 3,4-dibromo-5-methoxy-2(5*H*)-furanone **1a** and DMAP at room temperature for 30 min, the isolated yield of compound **A** is 95% (Scheme 3, eqn (2)). Compound **A** can further react with *p*-toluene sulfonylhydrazide **2a** to give the final product **3a** in isolated yield of 79% (eqn (3)). These imply that compound **A** should be a key intermediate during this process.

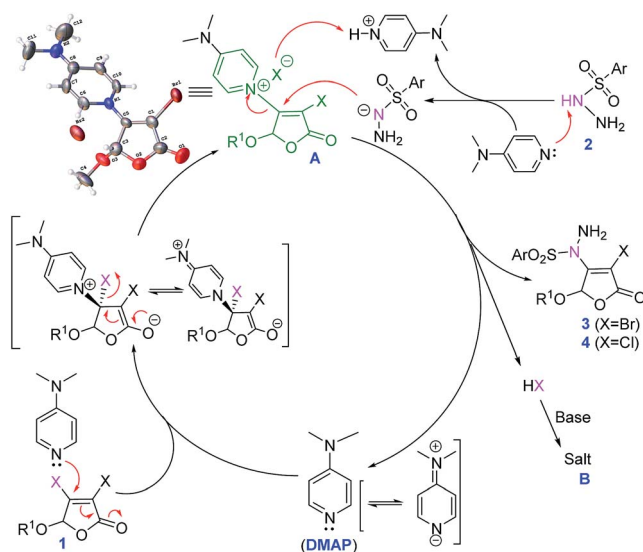
On the basis of the above experimental results and previous reports,¹⁷ the secondary nitrogen of sulfonyl hydrazides is regarded as a nonbasic amine maintaining its nucleophilicity. Thus, a possible nucleophilic substitution process based on the promotion mechanism of DMAP^{15,18} is proposed as illustrated in Scheme 4.

Firstly, 3,4-dihalo-2(5*H*)-furanone **1** reacts with DMAP to form the intermediate **A** by Michael addition–elimination. Then, **A** is attacked by sulfonyl hydrazides **2**, followed by the regeneration of DMAP and the formation of product **3** (or **4**). At the same time, HX as leaving compound is absorbed by DMAP to form salt **B**, which is transferred to the aqueous phase by



Scheme 3 Control experiments.





Scheme 4 Plausible reaction mechanism.

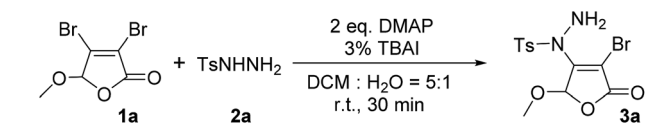
TBAI as phase transfer catalyst, further promoting the conversion. Therefore, DMAP plays dual roles as suitable organic base and key catalyst.

Scale-up application

It is significant to apply such a metal-free catalytic, effective, and easy-to-operate method into practical use, such as large-scale or industrial preparation. Using 3,4-dibromo-5-methoxy-2(5H)-furanone **1a** and *p*-toluene sulfonylhydrazide **2a** as model substrates for large-scale reaction under the standard conditions, the results are shown in Table 4.

It can be found that with the increase of the amount of reactant **1a** from 0.5 to 50 mmol stepwise, the yield of product

Table 4 Large-scale of 5-substituted 3,4-dihalo-2(5H)-furanones **1** and arylsulfonyl hydrazides **2**



Entry	Amount of 1a	Amount of 2a	Product 3a (g)	Yield ^a (%)
1	0.1349 g (0.5 mmol)	0.1116 g (0.6 mmol)	0.1544	82
2	1.3493 g (5 mmol)	1.1163 g (6 mmol)	1.5042	80
3	4.0783 g (15 mmol)	3.3489 g (18 mmol)	4.3995	78
4 ^b	8.1567 g (30 mmol)	6.6978 g (36 mmol)	8.4613	75
5 ^c	13.5945 g (50 mmol)	11.1629 g (60 mmol)	13.9123	74

 3l , 1.4829 g 76% ^d	 4c , 1.4962 g 80% ^d	 4h , 1.4192 g 72% ^d
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^a Isolated yield. ^b 1 h. ^c 2 h. ^d Amount of **1** (5.0 mmol) and **2** (6.0 mmol).

3a is gradually decreased. However, the yield of product **3a** can still reach to 74% (13.9123 g, Entry 5) even when the amount of **1a** is expanded by 100 times. Similarly, the other products, such as **3l**, **4c** and **4h**, can also be obtained by large scale preparation with good yields.

The above results not only may provide a new approach for the development of 2(5H)-furanone derivatives with potentially effective bioactivities. In addition, due to the existence of many reactive functional groups in these sulfonyl hydrazide products, the concise synthesis can be further extended in the future. For example, the free amino group on the sulfonyl hydrazide moiety may react with aldehydes and acyl halides to construct new carbon–nitrogen double bond or amide bond, which will promote the accessibility to the polyfunctionalized drug molecules.

Conclusions

In summary, the C–N coupling reaction of C_{sp2}–X compounds with arylsulfonyl hydrazides was achieved for the first time with good yields. The protocol shows excellent reaction site selectivity, which can realize coupling reaction of arylsulfonyl hydrazides at the secondary nitrogen atom, as well as good functional group tolerance for 2(5H)-furanone substrates, involving in a variety of complex structures, such as ester, ether, acetal units, lactone, aryl rings and C–X, C=C bonds. Importantly, the readily available C_{sp2}–X compounds, including low-reactive C_{sp2}–Cl compounds, are also suitable for this DMAP promoted method. Furthermore, the low cost of the reagents and wide range of substrates make this novel discovery as a powerful route for the synthesis of 2(5H)-furanone derivatives. Owing to the biological activity of sulfonyl hydrazides,¹⁹ the more derivatization synthesis and further biological activity assay are still in progress.

Experimental

General information

Melting point was performed on an X-5 digital melting point apparatus without correcting. ¹H, ¹³C and ¹⁹F NMR spectra were collected on a Varian AS600 spectrometer in CDCl₃ or D₂O using tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (HRMS) were obtained with a LCMS-IT-TOF mass spectrometer. Single-crystal X-ray analysis was obtained using Bruker APEX2 Smart CCD. TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF254) and visualization was effected at 254 nm. All reagents and solvents were purchased from commercial sources and used without further purification. Different 5-alkoxy (aryloxy) 3,4-dihalo-2(5H)-furanone intermediates were synthesized according to the literature procedure.¹¹

Experimental procedure for compounds **3a–3v**

The mixture of 3,4-dibromo-2(5H)-furanone **1** (0.50 mmol), DMAP (2.0 eq.), TBAI (3 mol%) and sulfonyl hydrazide **2** (0.60 mmol) in DCM : H₂O (3 mL, v : v = 5 : 1) was stirred at room



temperature for 10–30 min. After the completion of the reaction, the reaction mixture was quenched with H₂O (15 mL) and extracted with DCM (3 × 15 mL). Then, the organic layer was dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel to afford desired product.

Experimental procedure for compounds 4a–4s

The mixture of 3,4-dichloro-2(5H)-furanone **1** (0.50 mmol), DMAP (2.0 eq.), TBAI (3 mol%) and sulfonyl hydrazide **2** (0.60 mmol) in DCM : H₂O (3 mL, v : v = 5 : 1) was stirred at room temperature for 30–60 min. After the completion of the reaction, the reaction mixture was quenched with H₂O (15 mL) and extracted with DCM (3 × 15 mL). Then, the organic layer was dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel to afford desired product.

Experimental procedure for intermediate A

The mixture of 3,4-dibromo-5-methoxy-2(5H)-furanone **1** (0.50 mmol), and DMAP (2.0 eq.), in DCM (3 mL) was stirred at room temperature for 30 min. Once the reaction was complete, the evaporation of the solvents under reduced pressure gave a white solid. Then, the solid was recrystallized with DCM, and the pure intermediate **A** was obtained.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

- N. E. Campbell and G. M. Sammis, *Angew. Chem., Int. Ed.*, 2014, **53**, 6228.
- (a) K. Namba, K. Takeuchi, Y. Kaihara, M. Oda, A. Nakayama, A. Nakayama, M. Yoshida and K. Tanino, *Nat. Commun.*, 2015, **6**, 8731; (b) Z.-X. Huang, C.-P. Wang and G.-B. Dong, *Angew. Chem., Int. Ed.*, 2016, **55**, 5299; (c) Q. Sun, L.-G. Li, L.-Y. Liu, Q.-Q. Guan, Y. Yang, Z.-G. Zha and Z.-Y. Wang, *Org. Lett.*, 2018, **20**, 5592.
- (a) F. L. Yang, X. T. Ma and S. K. Tian, *Chem.–Eur. J.*, 2012, **18**, 1582; (b) O. Y. Yuen, C. M. So and F. Y. Kwong, *RSC Adv.*, 2016, **6**, 27584; (c) Y. H. Shang, *Appl. Organomet. Chem.*, 2018, **32**, e4484.
- (a) S.-Y. Li, X. Li, F. Yang and Y.-J. Wu, *Org. Chem. Front.*, 2015, **2**, 1076; (b) Y. Zhao, Y.-L. Lai, K.-S. Du, D.-Z. Lin and J.-M. Huang, *J. Org. Chem.*, 2017, **82**, 9655; (c) Z.-H. Peng, X. Zheng, Y.-J. Zhang, D.-L. An and W.-R. Dong, *Green Chem.*, 2018, **20**, 1760; (d) X.-T. Zhu, Q.-L. Lu, X. Wang, T.-S. Zhang, W.-J. Hao, S.-J. Tu and B. Jiang, *J. Org. Chem.*, 2018, **83**, 9890; (e) L.-X. Liu, K. Sun, L.-B. Su, J.-Y. Dong, L. Cheng, X. D. Zhu, C. T. Au, Y. B. Zhou and S. F. Yin, *Org. Lett.*, 2018, **20**, 4023; (f) J.-B. Ni, Y. Xue, L.-P. Sun and A. Zhang, *J. Org. Chem.*, 2018, **83**, 4598; (g) B. Yao, T. Miao, P. Li and L. Wang, *Org. Lett.*, 2019, **21**, 124.
- (a) G. Y. Zhang, S. S. Lv, A. Shoberu and J. P. Zou, *J. Org. Chem.*, 2017, **82**, 9801; (b) Q. Yu, Y. Yang, J.-P. Wan and Y. Liu, *J. Org. Chem.*, 2018, **83**, 11385; (c) Y.-S. Bao, X.-Q. Yang, Q.-F. Zhou and F. Yang, *Org. Lett.*, 2018, **20**, 1966; (d) Z. Yang, Y.-Q. Yan, A. Li, J.-S. Liao, L. Zhang, T. Yang and C.-S. Zhou, *New J. Chem.*, 2018, **42**, 14738; (e) Y.-L. Hou, L.-Y. Zhu, H. Hu, S.-W. Chen, Z.-F. Li, Y. J. Liu and P. Gong, *New J. Chem.*, 2018, **42**, 8752.
- (a) T. J. Donohoe, L. P. Fishlock, J. A. Basutto, J. F. Bower, P. A. Procopiou and A. L. Thompson, *Chem. Commun.*, 2009, 3008; (b) T. J. Donohoe, J. F. Bower, J. A. Basutto, L. P. Fishlock, P. A. Procopiou and C. K. A. Callens, *Tetrahedron*, 2009, **65**, 8969.
- N. Singh, R. Singh, D. S. Raghuvanshi and K. N. Singh, *Org. Lett.*, 2013, **15**, 5874.
- (a) X.-M. Wu and Y. Wang, *New J. Chem.*, 2018, **42**, 10953; (b) I. V. Ukrainets, A. A. Tkach, V. V. Kravtsova and S. V. Shishkina, *Chem. Heterocycl. Compd.*, 2008, **44**, 677.
- (a) B. Mao, M. Fananas-Mastral and B. L. Feringa, *Chem. Rev.*, 2017, **117**, 10502; (b) M. Yoritate, Y. Takahashi, H. Tajima, C. Ogihara, T. Yokoyama, Y. Soda, T. Oishi, T. Sato and N. Chida, *J. Am. Chem. Soc.*, 2017, **139**, 18386; (c) W.-Y. Qi, J.-X. Zhao, W.-J. Wei, K. Gao and J.-M. Yue, *J. Org. Chem.*, 2018, **83**, 1041; (d) S. Fujita, K. Nishikawa, T. Iwata, T. Tomiyama, H. Ikenaga, K. Matsumoto and M. Shindo, *Chem.–Eur. J.*, 2018, **24**, 1539.
- (a) N. Grimblat, T. S. Kaufman and A. M. Sarotti, *Org. Lett.*, 2016, **18**, 6420; (b) P. Yang, M. Yao, J. Li, Y. Li and A. Li, *Angew. Chem., Int. Ed.*, 2016, **55**, 6964; (c) Q. A. Castillo, J. Triana, J. L. Eiroa, L. Calcul, E. Rivera, L. Wojtas, J. M. Padron, L. Bobereth, M. Keramane, E. Abel-Santos, L. A. Baez and E. A. Germosen, *J. Nat. Prod.*, 2016, **79**, 907; (d) X. Li, P. H.-Y. Cheong and R. G. Carter, *Angew. Chem., Int. Ed.*, 2017, **56**, 1704; (e) B. Srinivas, D. S. Reddy, N. A. Mallampudi and D. K. Mohapatra, *Org. Lett.*, 2018, **20**, 6910; (f) M.-X. Wei, J. Zhang, F.-L. Ma, J.-Y. Yu, W. Luo and X.-Q. Li, *Eur. J. Med. Chem.*, 2018, **155**, 165.
- (a) Y.-C. Wu, S.-H. Luo, W.-J. Mei, L. Cao, H.-Q. Wu and Z.-Y. Wang, *Eur. J. Med. Chem.*, 2017, **139**, 84; (b) L. Cao, S.-H. Luo, H.-Q. Wu, L.-Q. Chen, K. Jiang, Z.-F. Hao and Z.-Y. Wang, *Adv. Synth. Catal.*, 2017, **359**, 2961; (c) Y.-C. Wu, L. Cao, W.-J. Mei, H.-Q. Wu, S.-H. Luo, H.-Y. Zhan and Z.-Y. Wang, *Chem. Biol. Drug Des.*, 2018, **92**, 1232; (d) L. Cao, J.-X. Li, H.-Q. Wu, K. Jiang, Z.-F. Hao,



- S.-H. Luo and Z.-Y. Wang, *ACS Sustainable Chem. Eng.*, 2018, **6**, 4147; (e) S.-H. Luo, K. Yang, J.-Y. Lin, J.-J. Gao, X.-Y. Wu and Z.-Y. Wang, *Org. Biomol. Chem.*, 2019, **17**, 5138; (f) H.-Q. Wu, K. Yang, S.-H. Luo, X.-Y. Wu, N. Wang, S.-H. Chen and Z.-Y. Wang, *Eur. J. Org. Chem.*, 2019, DOI: 10.1002/ejoc.201900749.
- 12 CCDC-1885760 (for **3a**) and 1885761 (for **A**), contain the supplementary crystallographic data for this paper.
- 13 (a) Y. Qin, L. H. Zhu and S. Z. Luo, *Chem. Rev.*, 2017, **117**, 9433; (b) Y.-B. Wang and B. Tan, *Acc. Chem. Res.*, 2018, **51**, 534; (c) T. Chanda and J. C.-G. Zhao, *Adv. Synth. Catal.*, 2018, **360**, 2; (d) W.-M. Mao, W. Shi, J. Li, D.-Y. Su, X.-M. Wang, L. Zhang, L. Pan, X. Wu and H.-X. Wu, *Angew. Chem., Int. Ed.*, 2019, **58**, 1106; (e) Q.-Q. Yang, X. Yin, X.-L. He, W. Du and Y.-C. Chen, *ACS Catal.*, 2019, **9**, 1258.
- 14 (a) A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi and K. Ishihara, *J. Am. Chem. Soc.*, 2007, **129**, 14775; (b) J. S. Quesnel, A. Fabrikant and B. A. Arndtsen, *Chem. Sci.*, 2016, **7**, 295; (c) Y. Ren, L.-G. Meng, T. Peng, L.-J. Zhu and L. Wang, *Adv. Synth. Catal.*, 2018, **360**, 3176; (d) B. Wang, Y. Wei, Z. J. Li, L. Pan and Y. S. Li, *ChemCatChem*, 2018, **10**, 5287.
- 15 L. W. Zeng, Z. C. Lai and S. L. Cui, *J. Org. Chem.*, 2018, **83**, 14834.
- 16 (a) L. Y. Zhu, P. P. Yan, L. Y. Zhang, Z. T. Chen, X. F. Zeng and G. F. Zhong, *RSC Adv.*, 2017, **7**, 51352; (b) J. Peng, J.-J. Xiang, H.-J. Wang, F.-B. Li, Y.-S. Huang, L. Liu, C. Y. Liu, A. M. Asiri and K. A. Alamry, *J. Org. Chem.*, 2017, **82**, 9751; (c) X. J. Zhang, A. Y. Xia, H. Y. Chen and Y. H. Liu, *Org. Lett.*, 2017, **19**, 2118; (d) H.-H. Kong, H.-L. Pan and M.-W. Ding, *J. Org. Chem.*, 2018, **83**, 12921.
- 17 (a) K. Namba, I. Shoji, M. Nishizawa and K. Tanino, *Org. Lett.*, 2009, **11**, 4970; (b) T. J. Donohoe, L. P. Fishlock, J. A. Basutto, J. F. Bower, P. A. Procopiou and A. L. Thompson, *Chem. Commun.*, 2009, 3008; (c) K. Namba, Y. Kaihara, H. Yamamoto, H. Imagawa, K. Tanino, R. M. Williams and M. Nishizawa, *Chem.-Eur. J.*, 2009, **15**, 6560; (d) T. J. Martin, V. G. Vakhshori, Y. S. Tran and O. Kwon, *Org. Lett.*, 2011, **13**, 2586.
- 18 (a) P. L. Lagueux-Tremblay, A. Fabrikant and B. A. Arndtsen, *ACS Catal.*, 2018, **8**, 5350; (b) A. Verma, S. Jana, C. D. Prasad, A. Yadav and S. Kumar, *Chem. Commun.*, 2016, **52**, 4179; (c) A. Polley, G. Bairy, P. Das and R. Jana, *Adv. Synth. Catal.*, 2018, **360**, 4161.
- 19 (a) S. Riaz, I. U. Khan, M. Bajda, M. Ashraf, Qurat-ul-Ain, A. Shaukat, T. U. Rehman, S. Mutahir, S. Hussain, G. Mustafa and M. Yar, *Bioorg. Chem.*, 2015, **63**, 64; (b) A. Kamal, M. N. A. Khan, K. S. Reddy and K. Rohini, *Bioorg. Med. Chem.*, 2007, **15**, 1004.

