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NIS-promoted three-component reaction of 3-oxo-3-arylpropanenitriles with arylsulfonyl hydrazides†

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A new three-component reaction of 3-oxo-3-arylpropanenitriles with arylsulfonyl hydrazides has been established, and an expanded inventory of 3-aryl-4-(arylthio)-1*H*-pyrazol-5-amines is synthesized by sequential cyclization and sulfenylation reactions under the action of NIS. In addition to the attractive features of multicomponent reactions, the protocol presents broad substrate scope, good functional group tolerance and mild reaction conditions. The utility of this procedure is further established by gram-scale synthesis as well as the diversified transformations of the products to useful compounds.

Introduction

Pyrazol-5-amines and their derivatives, an important class of five-membered-ring heterocycles with two adjacent nitrogen atoms, have exhibited a variety of pharmacological and biological activities and have been applied as pharmaceutical candidates (Fig. 1).[1–7] In addition, pyrazol-5-amines have wide industrial applications as inhibitors of corrosion on metals, such as Zn, Cu, Al and brass.[8] Up to now, various synthetic methods have been established to construct the 5-aminopyrazol skeleton.[9–20] In particular, the acid-catalyzed condensation of *β*-keto nitriles and hydrazines for the synthesis of 5-aminopyrazols has received considerable attention due to the advantages of mild reaction conditions, inexpensive and accessible raw materials, a wide range of substrates, and so on.[21] As a result, many poly-substituted heterocyclic compounds and fused heterocyclic compounds *via* 5-amino-pyrazoles have been achieved, such as bicyclic, tricyclic, tetracyclic and spiro-fused pyrazole derivatives.[22–26] However, successful examples of pyrazol-5-amines including the formation of C–S bonds are quite rare. In 2015, the Tu group reported the iodine-mediated three-component [3 + 2] annulation of *β*-ketonitriles, arylhydrazines and arylsulfonyl hydrazides to access richly decorated pyrazoles with a wide diversity in substituents (Scheme 1a).[27] Later, the same group developed a novel I_2-catalyzed multicomponent bicyclization reaction of *β*-ketonitriles with arylsulfonyl hydrazides to construct pyrazolo[1,5-*a*]pyrimidin-4-ium sulfonates. Besides, arylsulfonyl hydrazide was also successfully applied as an alternative sulfenylation agent (Scheme 1b).[28] Despite these elegant achievements, it is still highly desirable to develop new efficient methods to access pyrazol-5-amine derivatives. To the best of our knowledge, the efficient construction of 3-aryl-4-(arylthio)-1*H*-pyrazol-5-amines through multicomponent reactions of 3-oxo-3-arylpropanenitriles with two equivalents of arylsulfonyl hydrazides has not been realized. On the basis of our previous work,[29] herein we report a multicomponent reaction of *β*-ketonitriles with aryl-

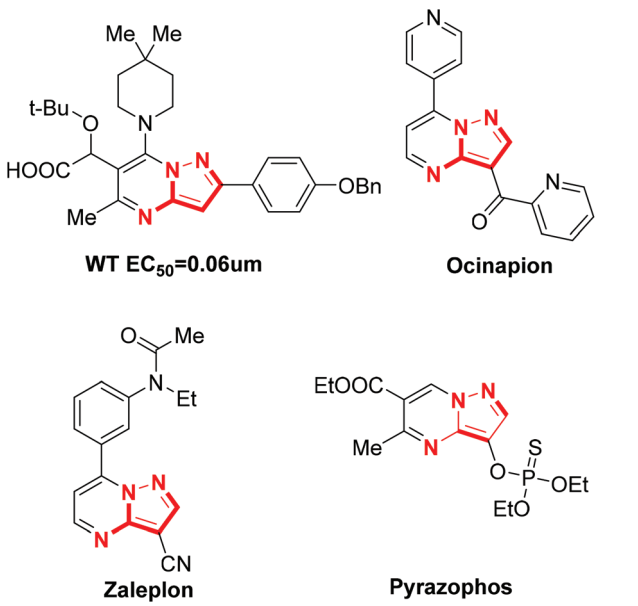

Fig. 1 Representative biologically active compounds with the pyrazol-5-amine motif.

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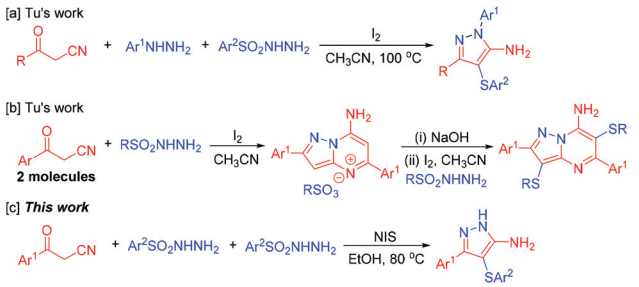
†CCDC 2035445, 2035449 and 2035452. For crystallographic data in CIF or other electronic formats see DOI: 10.1039/d1ob00438g



Scheme 1 Multicomponent reactions of β-ketonitriles with hydrazides.

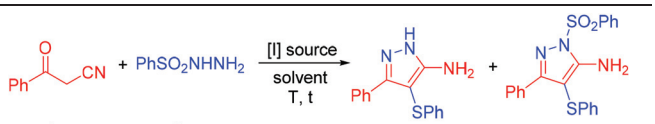
sulfonyl hydrazides to access 3-aryl-4-(arylthio)-1*H*-pyrazol-5-amine derivatives *via* sequence cyclization and sulfenylation reactions (Scheme 1c).

Results and discussion

Initially, we chose 0.3 mmol of 3-oxo-3-phenylpropanenitrile (**1a**) and 0.9 mmol of benzenesulfonyl hydrazide (**2a**) as model substrates to investigate the feasibility of this multi-component reaction (Table 1). When this reaction was performed at 100 °C in the presence of 2.0 equiv. of TBAI as the promoter and dipropylene glycol dimethyl ether (DPDME) as the solvent for 24 h, the cyclization and further sulfenylation reaction could occur smoothly and gave the corresponding products 3-phenyl-4-(phenylthio)-1*H*-pyrazol-5-amine (**3a**) and 3-phenyl-1-(phenylsulfonyl)-4-(phenylthio)-1*H*-pyrazol-5-amine (**4a**) in 40% and 30% yields, respectively. Encouraged by this result, we then investigated the effect of different solvents on the reaction (entries 2–6). The results showed that 1,4-dioxane and ethanol were effective for the reaction, but the conversion and selectivity of the reaction were not significantly improved (entries 2 and 3). In contrast, other solvents such as DMSO, acetonitrile (MeCN) and 1,2-dichloroethane (DCE) caused complete reaction inhibition (entries 4–6). From the perspective of environmental friendliness and cost, we chose ethanol as the solvent for further optimization of the conditions. When the reaction time was shortened to 12 hours, the conversion of the reaction was still maintained (entries 7 and 8). As the reaction temperature was reduced to 80 °C, the selectivity for the product **3a** was significantly improved (entries 9 and 10). Replacing TBAI with elemental iodine resulted in a lower yield of **3a** (entry 11). To our delight, the use of NIS as the iodine source provided the product **3a** in 88% yield without the formation of **4a** (entry 12). Compared with Tu's work,[28] this result showed that a suitable iodine source was critical for the selectivity of the multi-component reaction, in addition to controlling the ratio of the reactants. Moreover, the yield of **3a** was increased to 92% by reducing the loading of NIS to 0.5 equivalents (entry 13 *vs.* entries 14 and 15). Furthermore, lowering the reaction temperature to 60 °C resulted in an 89% yield of **3a** (entry 16). In addition, we found that a 91% yield could be obtained when the reaction time was shortened to 6 hours (entry 17). However, further shortening the time to 3 hours or reducing the amount of **2a** to 0.7 mmol led to a significant decrease in the yield of **3a** (entries 18 and 19). The structures of **3a** and **4a** were determined by single crystal X-ray diffraction (Fig. 2 and 3). At the same time, we found that the single crystal structure of **3a** contained two molecules of succinimide due to hydrogen bonding. Further studies showed that treating the organic extract with a dilute sodium hydroxide aqueous solution could break this intermolecular hydrogen bond to obtain the pure product **3a**.

Next, we investigated the scope of arylsulfonyl hydrazides (Table 2). The results showed that the electronic effects of the substituents on the aromatic ring of the substrate had no obvious influence on the reaction. Various functional groups, such as 4-substituted methyl, *tert*-butyl, methoxy, fluoro,

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a** **4a**

Entry	[I] (equiv.)	Solvent	T (°C)	t (h)	Yield[b] (%) 3a	4a
1	TBAI (2.0)	DPDME	100	24	40	30
2	TBAI (2.0)	1,4-Dioxane	100	24	44	37
3	TBAI (2.0)	EtOH	100	24	41	31
4	TBAI (2.0)	DMSO	100	24	Trace	Trace
5	TBAI (2.0)	MeCN	100	24	Trace	Trace
6	TBAI (2.0)	DCE	100	24	nr	nr
7	TBAI (2.0)	1,4-Dioxane	100	12	40	38
8	TBAI (2.0)	EtOH	100	12	41	42
9	TBAI (2.0)	EtOH	80	24	57	35
10	TBAI (2.0)	EtOH	80	12	55	35
11	I_2 (1.0)	EtOH	80	12	20	17
12	NIS (2.0)	EtOH	80	12	88	—
13	NIS (0.5)	EtOH	80	12	92	—
14	NIS (0.3)	EtOH	80	12	88	—
15	NIS (0.1)	EtOH	80	12	23	—
16	NIS (0.5)	EtOH	60	12	89	—
17	NIS (0.5)	EtOH	80	6	91	—
18	NIS (0.5)	EtOH	80	3	86	—
19[c]	NIS (0.5)	EtOH	80	6	83	—

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), solvent (0.5 mL), under air. [b] Isolated yield. [c] **1a** (0.3 mmol), **2a** (0.7 mmol).

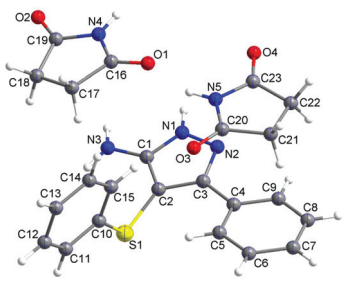


Fig. 2 The crystal structure of **3a** (CCDC: 2035449).†

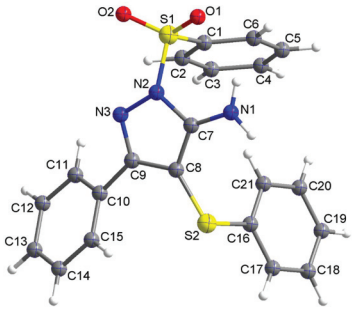
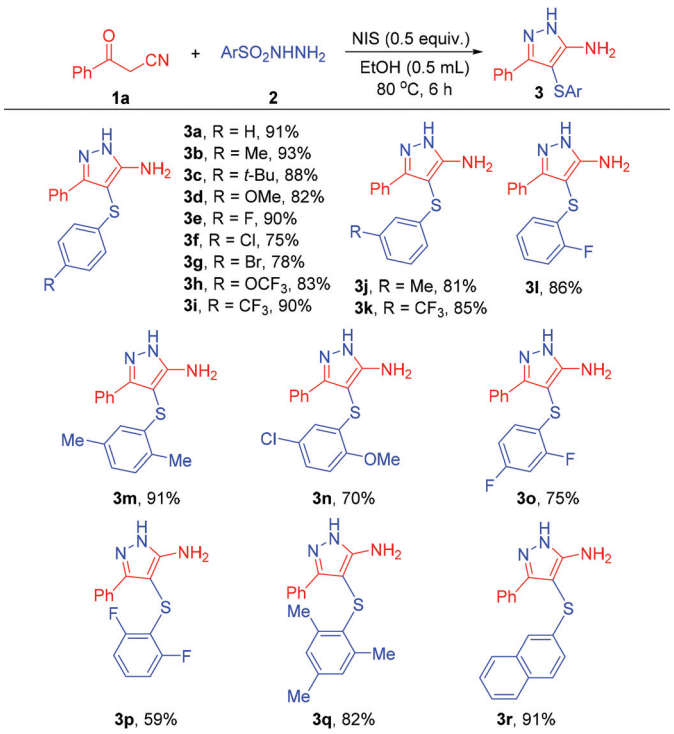


Fig. 3 The crystal structure of **4a** (CCDC: 2035445).†

Table 2 NIS-mediated reactions of **1a** with arylsulfonyl hydrazides[a]



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), NIS (0.5 equiv.), EtOH (0.5 mL), under air, 80 °C, 6 h; isolated yield.

chloro, bromo, trifluoromethyl, and trifluoromethoxy, were all tolerated well, leading to the desired products **3b–3i** in 75–93% yields. The structure of **3i** was determined by single crystal X-ray diffraction (Fig. 4). Furthermore, the substrates containing 3-Me and 3-CF_3 groups could also be successfully transformed into the target products **3j** and **3k**, respectively, with good yields. To our delight, the sterically congested substrates were good candidates as well, and the reactions were successful for both electron-donating and electron-withdrawing substituents on the aromatic rings, affording the desired products **3l–3q** in 59–91% yields. In addition, naphthalene-2-sulfonohydrazide performed also quite well in the transformation, and the product **3r** was obtained in a 91% yield.

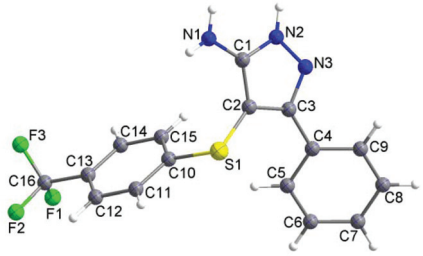
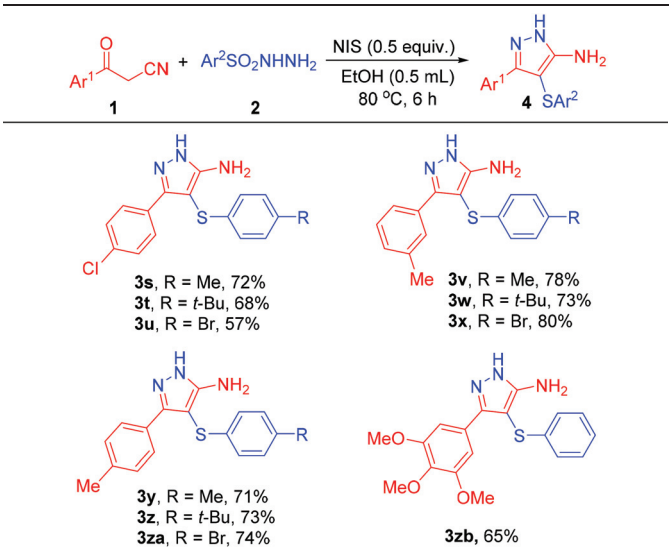


Fig. 4 The crystal structure of **3i** (CCDC: 2035452).†

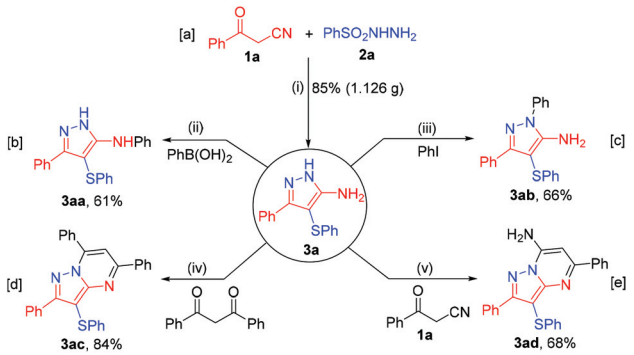
To further display the synthetic utility of the reaction, we thoroughly investigated the reactions of 3-oxo-3-arylpropanenitriles and arylsulfonyl hydrazides. As shown in Table 3, 3-(4-chlorophenyl)-3-oxopropanenitrile reacted smoothly with various arylsulfonyl hydrazides to obtain the products **3s–3u** in 57–72% yields. Meanwhile, the reactions of 3-oxo-3-(*m*- or *p*-tolyl)propanenitrile with arylsulfonyl hydrazides also proceeded very well, providing the desired products **3v–3za** in 71–80% yields. Gratifyingly, the reaction was compatible with some substituted 3-oxo-3-arylpropanenitriles such as 3-oxo-3-(3,4,5-trimethoxyphenyl)propanenitrile, generating the product **3zb** in a 65% yield.

To demonstrate the synthetic utility of this reaction, a gram-scale reaction of **1a** (5 mmol) and **2a** (15 mmol) was performed under the optimized conditions. The product **3a** was formed in an 85% yield (1.126 g, Scheme 2a) and the NIS was recovered in an 85% yield (0.486 g). Furthermore, the synthetic transformations of **3a** were investigated to extend the application of this product. It is worth mentioning that the regioselective C–N coupling reaction of **3a** with phenylboronic acid or iodobenzene can proceed smoothly by adjusting the cata-

Table 3 NIS-mediated reactions of **1** with arylsulfonyl hydrazides[a]



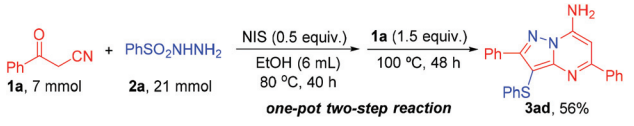
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), NIS (0.5 equiv.), EtOH (0.5 mL), under air, 80 °C, 6 h; isolated yield.



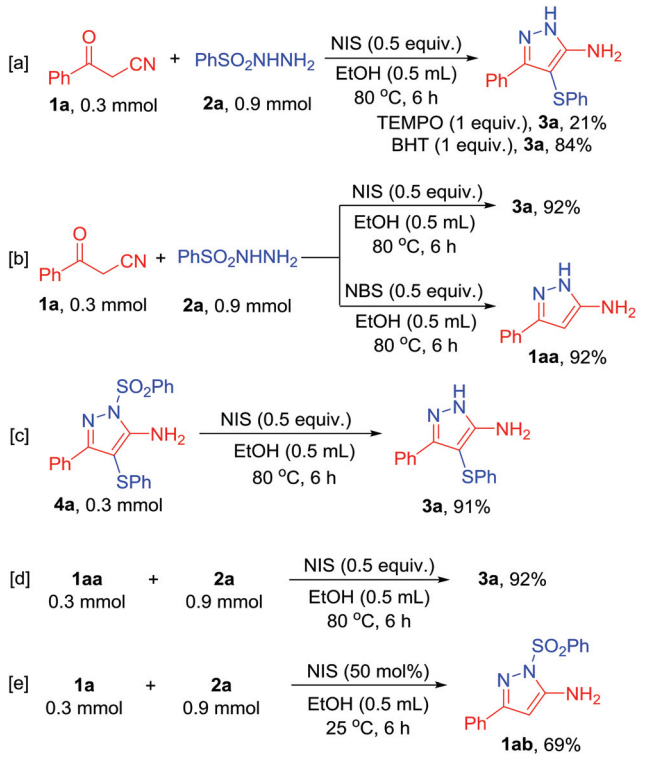
Scheme 2 Gram-scale synthesis and transformations of **3a**. Reaction conditions: (i) **1a** (5 mmol), **2a** (15 mmol), NIS (0.5 equiv.), EtOH (5 mL), 80 °C, 36 h; (ii) **3a** (0.3 mmol), $PhB(OH)_2$ (0.3 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (20 mol%), DBU (2 equiv.), DMSO (1 mL), 50 °C, 10 h; (iii) **3a** (0.3 mmol), PhI (0.45 mmol), Cu_2O (10 mol%), KOH (2 equiv.), DMSO (1 mL), 120 °C, 14 h, under N_2 atmosphere; (iv) **3a** (0.3 mmol), 1,3-diphenylpropane-1,3-dione (0.6 mmol), HOAc (1 mL), 80 °C, 12 h; (v) **3a** (0.2 mmol), **1a** (0.3 mmol), I_2 (20 mol%), EtOH (2 mL), 100 °C, 12 h.

lytic conditions, and the *N*-arylation products **3aa** and **3ab** are obtained in yields of 61% and 66%, respectively (Scheme 2b and c). In addition, **3a** can undergo a cyclization reaction with 1,3-diphenylpropane-1,3-dione under acidic conditions, affording the fused heterocyclic product **3ac** in an 84% yield (Scheme 2d). Similarly, the reaction of **3a** and 3-oxo-3-phenylpropanenitrile (**1a**) in the presence of I_2 can also be enabled to work effectively, leading to a 68% yield of the product **3ad**. Further research found that the synthesis of product **3ad** could also be achieved through a one-pot two-step reaction (Scheme 3). This synthetic strategy for mono-arylthio substituted pyrazolo[1,5-*a*]pyrimidine is a good supplement to the reported I_2-catalyzed disulfenylation of pyrazolo[1,5-*a*]pyrimidines.[28]

To investigate the reaction mechanism, we carried out a series of control experiments (Scheme 4). In the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-*tert*-butyl-4-methylphenol), the NIS-promoted reaction of **1a** with **2a** was not suppressed, and the product **3a** was obtained in 21% and 84% yields, respectively (Scheme 4a). The result shows that a free radical pathway is not involved in the transformation process. When NBS replaces NIS as a promoter, the product **3a** is not obtained, but the product 3-phenyl-1*H*-pyrazol-5-amine **1aa** is provided (Scheme 4b). This fact indicates that NIS is involved in this sulfenylation reaction. Treatment of **4a** under standard conditions successfully affords the desired product **3a** with excellent yields, which further confirms that NIS plays a vital role in the removal of



Scheme 3 Synthesis of **3ad** *via* a one-pot two-step reaction.

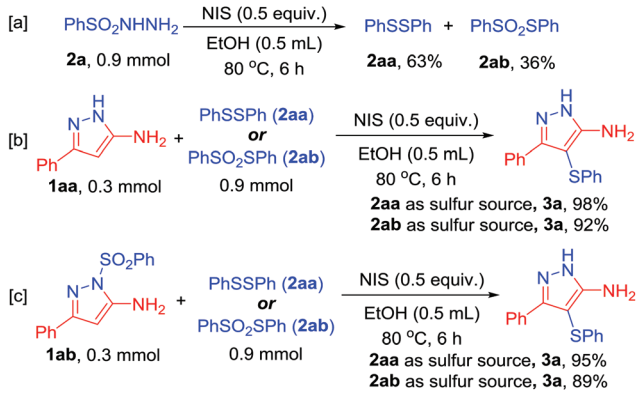


Scheme 4 Control experiments.

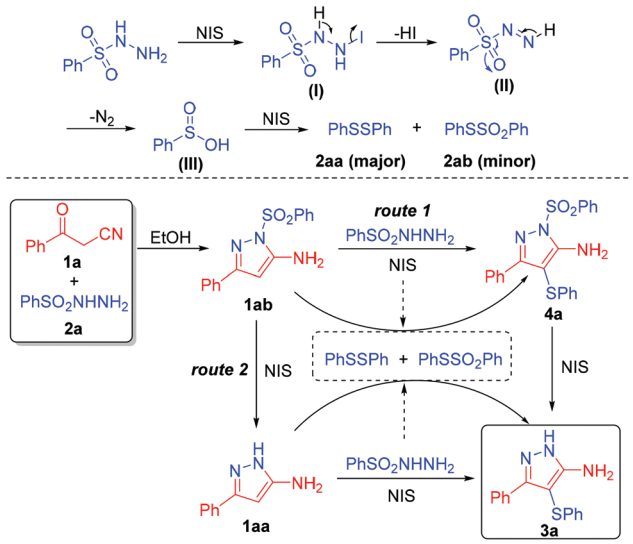
the phenylsulfonyl group (Scheme 4c). Furthermore, we found that the reaction of **1aa** and **2a** could proceed smoothly under the optimized conditions (Scheme 4d). This phenomenon indicates that **1aa** may be an important intermediate in this sulfenylation. Notably, the reaction of **1a** and **2a** at room temperature can be effectively controlled to produce the corresponding cyclizated product **1ab** in a 69% yield, and the subsequent sulfenylated reaction did not proceed (Scheme 4e). This result suggests that **1ab** may be another important intermediate in the whole reaction.

Next, the benzenesulfonohydrazide was treated under optimized conditions, affording the corresponding products sulfinothioyldibenzene and *S*-phenyl benzenesulfonothioate in 63% and 36% yields, respectively (Scheme 5a). This observation implies that sulfinothioyldibenzene and *S*-phenyl benzenesulfonothioate may be important intermediates generated during the sulfenylation reaction. Treatment of **1aa** or **1ab** with sulfinothioyldibenzene or *S*-phenyl benzenesulfonothioate could successfully provide the desired product **3a** in excellent yields, which further confirms our above speculation (Scheme 5b and c).

Based on the above experimental results and the related publications,[30,31] a possible mechanistic pathway is depicted (Scheme 6). The reaction is initiated by the reduction of $PhSO_2NHNH_2$ in the presence of NIS, which subsequently goes through the intermediates (**I** and **II**) to form benzenesulfinic acid (**III**). Subsequently, the intermediate (**III**) is further transformed into 1,2-diphenyldisulfane (**2aa**) and *S*-phenyl benzene-



Scheme 5 Possible arylthio intermediates.



Scheme 6 Proposed reaction mechanism.

sulfonothioate (**2ab**) under the action of NIS.[32] On the other hand, **1a** reacts with **2a** to form the product **1ab**. Next, the sulfenylation of **1ab** is mainly achieved through the following two routes: (i) **route 1**: **1ab** undergoes electrophilic substitution with $PhSO_2NHNH_2$ (**2a**) to give the product **4a**. Further treatment of **4a** with NIS provides the final product **3a**; (ii) **route 2**: the intermediate **1ab** generated can be converted into **1aa** in the presence of NIS. Subsequently, **1aa** reacts with $PhSO_2NHNH_2$ (**2a**) to furnish the final product **3a**.

Conclusions

In summary, we have realized the application of arylsulfonyl hydrazides as dual-functional reagents in a three-component reaction. Consequently, this protocol provides simplified flexible access to 3-aryl-4-(arylthio)-1*H*-pyrazol-5-amines from 3-oxo-3-arylpropanenitriles and arylsulfonyl hydrazides. The procedure involves sequences consisting of cyclization, sulfenylation and the removal of arylsulfonyl in the presence of NIS. The characteristics of broad substrate scope, reliable scalability, and flexibility of structural modification make this strategy a powerful tool for designing multifunctional *N*-heterocyclic scaffolds with biomedical significance. We believe that this approach may be valuable for seeking synthetic fragments with unique activities for drug research.

Experimental

General procedure for NIS-mediated reactions of 3-oxo-3-arylpropanenitriles with arylsulfonyl hydrazides

A mixture of 3-oxo-3-arylpropanenitrile (**1**, 0.3 mmol), arylsulfonyl hydrazide (**2**, 0.9 mmol), NIS (0.15 mmol), and EtOH (0.5 mL) was added into a reaction tube. The solution was stirred and heated to 80 °C for 6 h. After completion of the reaction, the solvent (EtOH) was removed under reduced pressure. The residue was treated with sodium hydroxide aqueous solution (0.2%, 6 mL) and extracted with dichloromethane (10 mL × 5), and the organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on basic Al_2O_3 using dichloromethane/ethanol (50 : 1) as the eluent to afford the product **3**.

General procedure for gram-scale experiment of 3a

A mixture of 3-oxo-3-phenylpropanenitrile (**1a**, 5 mmol), benzenesulfonyl hydrazide (15 mmol), NIS (2.5 mmol) and EtOH (5 mL) was added into a reaction tube. The solution was stirred and heated to 80 °C for 36 h in air. After completion of the reaction, the solvent (EtOH) was removed under reduced pressure. The residue was dissolved in dichloromethane (8 mL). After the solution was left for 2 hours, the precipitated solid was filtered and washed with dichloromethane (15 mL × 3) to recover NIS with an 85% yield (0.486 g). The organic phase was extracted with an aqueous solution of 0.2% NaOH (15 mL), and the dichloromethane solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on basic Al_2O_3 using dichloromethane/ethanol (50 : 1) as the eluent to afford the product **3a** in an 85% yield (1.126 g).

Typical procedure for the synthesis of 3aa

A mixture of **3a** (0.3 mmol), $PhB(OH)_2$ (0.3 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.06 mmol), DBU (0.6 mmol) and DMSO (1 mL) was added into a reaction tube. The solution was stirred and heated to 50 °C for 10 h. After completion of the reaction, the mixture was quenched with a saturated solution of NaCl (5 mL) and extracted with EtOAc (10 mL × 3). The combined EtOAc extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using PE/EtOAc (5 : 1) as the eluent to afford the product **3aa** in a 61% yield (62.8 mg).

Typical procedure for the synthesis of 3ab

A mixture of **3a** (0.3 mmol), PhI (0.45 mmol), Cu_2O (0.02 mmol), KOH (0.6 mmol) and DMSO (1 mL) was added into a reaction tube. The solution was stirred and heated to 120 °C for 14 h in a N_2 atmosphere. After completion of the reaction, the mixture was quenched with a saturated solution of NaCl (5 mL) and extracted with EtOAc (10 mL × 3). The combined EtOAc extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using PE/EtOAc (5 : 1) as the eluent to afford the product **3ab** in a 66% yield (67.9 mg).

Typical procedure for the synthesis of 3ac

A mixture of **3a** (0.3 mmol), 1,3-diphenyl-1,3-propanedione (0.6 mmol) and AcOH (1 mL) was added into a reaction tube. The solution was stirred and heated to 80 °C for 12 h. After completion of the reaction, the mixture was quenched with a saturated solution of NaCl (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using PE/EtOAc (10 : 1) as the eluent to afford the product **3ac** in an 84% yield (113.5 mg).

Typical procedure for the synthesis of 3ad

A mixture of **3a** (0.2 mmol), 3-oxo-3-phenylpropanenitrile (**1a**, 0.3 mmol), I_2 (20 mol%) and EtOH (2 mL) was added into a reaction tube. The solution was stirred and heated to 100 °C for 12 h. After completion of the reaction, the solvent (EtOH) was removed under reduced pressure. The residue was treated with a saturated solution of NaCl (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using PE/EtOAc (10 : 1) as the eluent to afford the product **3ad** in a 68% yield (53.5 mg).

Typical procedure for the synthesis of 3ad *via* a one-pot two-step reaction

A mixture of 3-oxo-3-phenylpropanenitrile (**1a**, 7 mmol), benzenesulfonyl hydrazide (21 mmol), NIS (3.5 mmol), and EtOH (6 mL) was added into a reaction tube. The solution was stirred and heated to 80 °C for 40 h in air. After completion of the reaction, 3-oxo-3-phenylpropanenitrile (**1a**, 10.5 mmol) was added. The solution was stirred and heated to 100 °C for 48 h. After completion of the reaction, the solvent (EtOH) was removed under reduced pressure. The residue was treated with a saturated solution of NaCl (30 mL) and extracted with CH_2Cl_2 (35 mL × 3). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using PE/EtOAc (10 : 1) as the eluent to afford the product **3ad** in a 56% yield (1.546 mg).

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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