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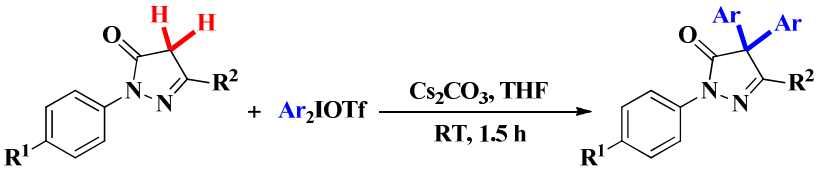
A novel and efficient one-pot sequential C4-diarylation of pyrazolin-5-ones with diaryliodonium salts at room temperature in absence of metal catalyst was reported.



✓ Metal free ✓ Mild reaction conditions ✓ Good to high yields

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Metal-free one-pot sequential direct diarylation of pyrazolin-5-ones with diaryliodonium salts

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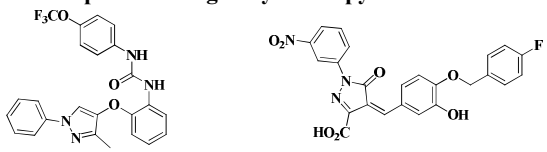
A novel and efficient one-pot sequential C4-diarylation of pyrazolin-5-ones with diaryliodonium salts in absence of metal catalyst was reported. A variety of C4-diarylated pyrazolin-5-one derivatives were obtained in good to high yields under mild conditions.

Diaryliodonium salts (Ar_2IX) are versatile electrophilic arylating agents and have been broadly used in organic synthesis due to their high reactivity, stable nature, easiness to handle and readily availability.[1] The metal-catalyzed or metal-free *C*-arylation of arenes and heteroarenes,[2] *N*-arylation of secondary anilines and amides,[3] *O*-arylation of aliphatic alcohols, phenols and carboxylic acids [4] with diaryliodonium salts have become powerful methods for the rapid construction of C–C bond, C–N bond and C–O bond, respectively.

The direct activation and functionalization of the inert aromatic and heteroaromatic C–H bond without the prefunctionalization of substrates have been considered as one of the most challenging goals in organic synthesis.[5] Diaryliodonium salts exhibited extraordinary reactivity toward less reactive Csp^2–H bond in heterocycles both in the absence and presence of metal transition catalyst.[6] For example, in 2012, Zhang and Yu developed a novel transition metal-free direct C-2 arylation of pyrrole with diaryliodonium salts.[7] Ackermann reported an unprecedented metal-free C-2 arylation of artificial indoles with diaryliodonium salts.[8] Direct C−H arylation of quinones and naphthoquinones was also achieved with diaryliodonium salts under mild and metal-free conditions.[9] More recently, Wang has successfully developed the highly efficient metal-free C4-arylation of 4-substituted-pyrazolin-5-ones with diaryliodonium salts using 4-dimethylaminopyridine (DMAP) as base and toluene as solvent.[10]

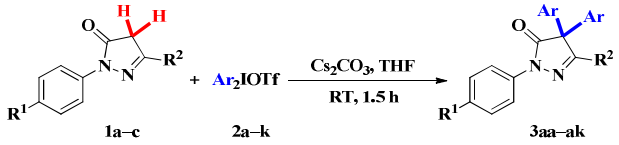
Pyrazolinones, the five-membered-ring lactams, are often found as structural subunits in medicinal chemistry and agrochemical chemistry (Figure 1).[11] They also serve as versatile nucleophiles in organic synthesis for the preparation of complex molecules because they have two nucleophile sites, one is carbon anion and another is oxygen anion.[12] Recently, selective functionalization of pyrazolin-5-ones at the C-4 position has attracted much attention.[13] However, the introduction of two bulky substituents such as aryl group at C-4 position of pyrazolin-5-ones in a one-pot process has rarely been explored.[14] In this communication, we report a one-pot protocol for direct C–H bond diarylation of pyrazolin-5-ones with diaryliodonium salts under the assistance of Cs_2CO_3 at room temperature without any additional metal catalyst (Scheme 1).

Figure 1 Examples of biologically active pyrazolinone derivatives



P2Y1 receptor antagonist HIV-1 integrase inhibitor

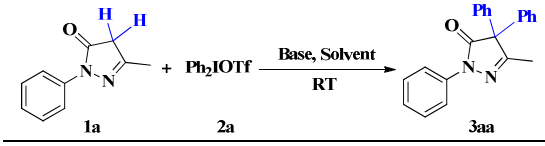
Scheme 1 Diarylation of pyrazolin-5-ones with diaryliodonium salts



1a–c 2a–k 3aa–ak

In our initial study, the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **1a** with diphenyliodonium triflate **2a** was conducted to screen the reaction conditions (Table 1). The results indicated that most solvents could provide excellent yields of diphenylated product **3aa** (entries 1–8), except for water (entry 9). Considering THF as a readily available, economical, and environmentally friendly solvent, we selected it as solvent to perform this one-pot sequential diarylation reaction. To our delight, the reaction was finished within 1.5 h to give excellent yield of **3aa** (99%, entry 11). Further screening of bases revealed that the transformation could also proceed efficiently in presence of different bases such as K_2CO_3, *t*BuOK, and NaOH (entries 14−16), and Cs_2CO_3 is the optimal base (entry 11). No reaction was observed in the absence of base (entry 13). Subsequently, the effect of the anion in iodonium salts was evaluated. Both diphenyliodonium tetrafluoroborate (Ph_2IBF_4) and diphenyliodonium *p*-toluenesulfonate (Ph_2IOTs) were also reacted under the optimal conditions (entry 11) to afford the desired product **3aa** in excellent (entries 17 and 18). It is very interesting that no monophenylated byproduct was detected in all cases even when decreasing the amount of **2a** to 1.0 equiv or reaction temperature to –20 °C, respectively.

Table 1 Optimization of reaction conditions[a]

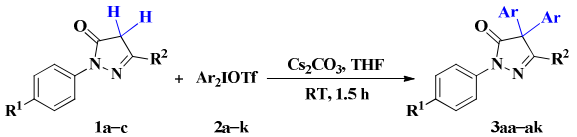


1a 2a 3aa

Entry	Base	Solvent	Reaction Time (h)	Yield of **3aa**[b] (%)
1	Cs_2CO_3	DMSO	4.0	98
2	Cs_2CO_3	DMF	4.0	96
3	Cs_2CO_3	THF	4.0	99
4	Cs_2CO_3	CH_3CN	4.0	93
5	Cs_2CO_3	NMP	4.0	97
6	Cs_2CO_3	Toluene	4.0	94
7	Cs_2CO_3	Dioxane	4.0	99
8	Cs_2CO_3	CH_2Cl_2	4.0	97
9	Cs_2CO_3	H_2O	4.0	0
10	Cs_2CO_3	THF	2.0	99
11	Cs_2CO_3	THF	1.5	99
12	Cs_2CO_3	THF	1.0	91
13	None	THF	1.5	0
14	K_2CO_3	THF	1.5	70
15	*t*BuOK	THF	1.5	85
16	NaOH	THF	1.5	95
17[c]	Cs_2CO_3	THF	1.5	98
18[d]	Cs_2CO_3	THF	1.5	95

[a] *Reagents and conditions:* **1a** (0.25 mmol), **2a** (0.525 mmol, 2.1 equiv**)**, base (0.525 mmol, 2.1 equiv), solvent (2 mL), room temperature. [b] Yields determined by GC analysis and based on **1a**. [c] Ph_2IOTs was used. [d] Ph_2IBF_4 was used.

Table 2 Diarylation of pyrazolinones with various symmetrical diaryliodonium salts[a]



1a–c 2a–k 3aa–ak

Entry	R^1	R^2	Ar	**3**	Yield (%)[b]
1	H	Me	Ph	**3aa**	90
2	H	Me	4-FC_6H_4	**3ab**	92
3	H	Me	4-ClC_6H_4	**3ac**	83
4	H	Me	4-BrC_6H_4	**3ad**	80
5	H	Me	4-MeC_6H_4	**3ae**	86
6	H	Me	4-$MeOC_6H_4$	**3af**	80[c]
7	H	Me	4-$CF_3C_6H_4$	**3ag**	91[d]
9	F	Me	Ph	**3ba**	82
10	F	Me	4-BrC_6H_4	**3bd**	77
11	F	Me	4-$MeOC_6H_4$	**3bf**	75
12	H	Ph	Ph	**3ca**	90
13	H	Ph	4-FC_6H_4	**3cb**	91
14	H	Ph	4-$MeOC_6H_4$	**3cf**	81
15	H	Me	3-MeC_6H_4	**3ah**	28[e]
16	H	Me	2,5-$Me_2C_6H_3$	**3ai**	trace
17	H	Me	Mesityl	**3aj**	trace
18	H	Me	2-Thienyl	**3ak**	trace

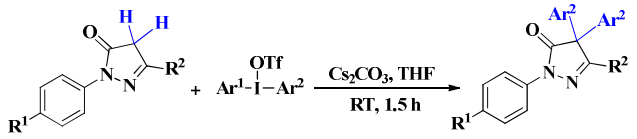
[a] *Reaction conditions:* **1a–c** (0.5 mmol), symmetrical diaryliodonium salts **2a–k** (1.05 mmol, 2.1 equiv), Cs_2CO_3 (1.05 mmol, 2.1 equiv), THF (4 mL). [b] Isolated yield. [c] (4-$MeOC_6H_4)_2IOTs$ was used. [d] (4-$CF_3C_6H_4)_2IBF_4$ was used. [e] GC-MS analysis.

With the optimized reaction conditions in hand (Table 1, entry 11), we next investigated the performance of various diaryliodonium triflates for the direct diarylation of pyrazolinones (Table 2 and 3). As shown in Table 2, most symmetrical diaryliodonium salts with electron-withdrawing groups (F, Cl, Br, CF_3) (for example entries 2–4, 7) or with electron-neutral group (entry 1) could afford the diarylated products in good to excellent yields and no monoarylated byproduct was observed. Although diaryliodonium salt with electron-donating substituents (CH_3, CH_3O) also underwent diarylation in good yields (entries 5, 6, 11), a small or trace amount of monoarylated byproduct was detected. The position of the substituent on the diaryliodonium salts played a key role in this reaction. Generally, diaryliodonium salts possessing substituent in the *para*-position on the benzene ring proceeded well. However, when *ortho*- or *meta*-substituted diaryliodonium salts were used as the aryl sources, the diarylation reaction did not proceed efficiently and only small or trace amounts of the desired products were observed (entries 15–17) due to the steric effect of the substituent attached at the *ortho*- or *meta*- position. Unfortunately, almost no reaction took place with [(2-thienyl)$_2$I]OTf as the coupling partner (entry 18). In addition, the results indicated that the substituents (R^1 and R^2) in pyrazolinones **1a–c** had no obvious influence on the yields of the products (for example **3aa** *versus* **3ca**).

The reactions of unsymmetrical diaryliodonium salts with pyrazolinones were also investigated (Table 3). It was found that with unsymmetrical diaryliodonium salts (**2l**, entry 1 and **2m**, entries 2–3), the more electron-poor aryl moiety was selectively transferred to the products. In case of arylmesityl iodonium salts, only 4-trifluoromethylphenyl group in **2n** (entry 4) or phenyl group in **2o** (entry 5) was introduced into the arylated products due to the steric hindrance of the mesityl group. When [(Ph)I(2-thienyl)]OTf (**2p**, entry 6) was used as the coupling partner, transfer of the phenyl group was favored and the diphenylated product **3aa** was obtained as major product.

Generally, diaryliodonium salts react with nucleophiles via either a polar or radical pathway.[3c, 15] Furthermore, the α-arylation of carbonyl compounds may follow an ionic or radical mechanism depending on the substrates and reaction conditions.[2b, 9, 16] To gain some mechanistic insight into the diarylation of pyrazolin-5-ones with diaryliodonium salts, two comparative experiments were performed using the

Table 3 Diarylation of pyrazolinones with various unsymmetrical diaryliodonium salts[a]

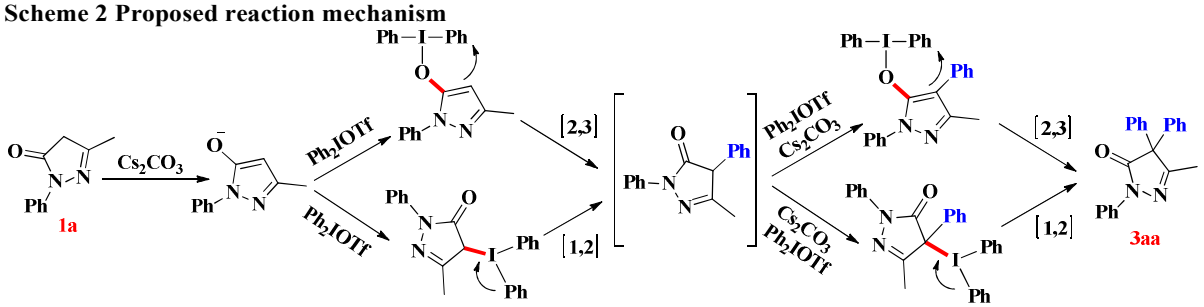


1a, 1c 2l–p 3aa, 3ag, 3cg, 3al

Entry	R^1	R^2	Ar^1	Ar^2	Product **3**	Yield (%)[b]
1	H	Me	4-$OMeC_6H_4$	4-$NO_2C_6H_4$	**3al**	87
2	H	Me	4-$OMeC_6H_4$	4-$CF_3C_6H_4$	**3ag**	85
3	H	Ph	4-$OMeC_6H_4$	4-$CF_3C_6H_4$	**3cg**	83
4	H	Me	Mesityl	4-$CF_3C_6H_4$	**3ag**	78
5	H	Me	Mesityl	Ph	**3aa**	73
6	H	Me	2-Thienyl	Ph	**3aa**	89

[a] *Reaction conditions:* **1a**, **1c** (0.5 mmol, 1.0 equiv), unsymmetrical diaryliodonium salts **2l–p** (1.05 mmol, 2.1 equiv), Cs_2CO_3 (1.05 mmol, 2.1 equiv), THF (4 mL). [b] Isolated yield.

Scheme 2 Proposed reaction mechanism



model reaction under the standard reaction conditions. When the reaction of **1a** with **2a** was performed in the presence of one equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical scavenger, or one equivalent of the free neutral radical galvinoxyl, the reactions proceeded smoothly and provided the desired product **3aa** in high yields (95% and 85%, respectively). Based on these results, a radical-type mechanism for the diarylation reaction can be ruled out. Therefore, we suggest that the mechanism of this diarylation probably includes the initial formation of the O–I bond or C–I bond, followed by reductive elimination of PhI to afford product **3aa** via [2, 3]- or [1, 2]-rearrangement, respectively (Scheme 2, with **1a** as the example).[2b, 3c, 16a, 16b] It should be noted that attempts to isolate the monoarylated products were unsuccessful because only small or trace amount of them formed.

In summary, we have developed an efficient and straightforward synthetic protocol for C4-diarylation of pyrazolin-5-ones with diaryliodonium salts. The reaction proceeded efficiently under metal-free conditions at room temperature and afforded the corresponding diarylated products in high yields. The use of environmentally friendly solvent (THF *versus* toluene) and economical base (Cs_2CO_3 *versus* DMAP) makes the process more useful and practical. Based on preliminary mechanistic studies, we could rule out a radical mechanism and suggest a reductive elimination pathway for the diarylation reaction.

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Notes and references

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†*Electronic supplementary information (ESI) available: General procedure for synthesis, characterization data, and ^1H, ^{13}C, ^{19}F NMR, IR and HRMS spectra of compounds **3**. See DOI: xxxxxxxxxx*

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