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Pd-Catalyzed Coupling of Thioamides with *N*-Tosylhydrazones/ Trapping by Esters Cascade Reaction

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ABSTRACT: *N*,*N*-Disubstituted thioamides coupled with *N*-tosylhydrazones under $Pd(TFA)_2/{}^tBuXPhos$ catalyst and NaO^tBu, and the intermediates from palladium carbene migratory insertion containing β -hydrogen were trapped by intramolecular esters activated by $BF_3 \cdot Et_2O$ instead of undergoing β -H elimination, providing polyfunctional thiophen-3(2H)-ones with sulfur-containing tetrasubstituted carbon centers in moderate to good yields. The reaction features the formation of three bonds in a single operation, odorless, safe, and easily available substrates, wide substrate scope, and excellent functional group tolerance.

 ${f S}$ ulfur-containing heterocycles exist widely in natural products, drugs, biological compounds, and materials.¹ Odorless, nontoxic, and easily available starting materials for preparing sulfur-containing heterocycles are highly desirable. Recently, we reported the ready synthesis of N,N-disubstituted thioamides bearing α, α -diesters from malonate esters and thiocarbamoyl fluorides² in which the sulfur atom was derived from sulfur (S_8) .³ Thioamides, which are odorless and nontoxic/low toxic, have been widely used to synthesize sulfur-containing heterocycles via intramolecular coupling reactions including C-H functionalizations.^{2,4} Metal-catalyzed intramolecular or intermolecular reactions of thioamides with hydrazones or α -diazocarbonyl compounds to transform C=S to C=C bonds have also been reported.⁵ However, intermolecular reactions involving thioamides in a single operation for the construction of complex and diversified heterocycles with sulfur-containing tetrasubstituted carbon centers are underdeveloped. Sulfur heterocycles in this class exist in natural products such as thiolactomycin and thiotetroamide as well as in biological compounds demonstrat-ing anticancer,^{1d} weight loss,^{1d} antibacterial,^{6a-c} antimalarial,^{6d,e} antituberculosis,^{6f,g} and pesticidal activities.^{6h}

The Hu group pioneered the development of a series of multicomponent reactions of trapping of ylides or zwitterionic intermediates derived from nucleophiles and diazocarbonyl compounds by electrophiles such as aldehydes, ketones, imines, or α , β -unsaturated compounds to form tetrasubstituted carbon centers.⁷ The challenge of these methods lies in the 1,2-proton transfer in the active intermediates. Esters have never

been documented to realize the trapping of active intermediates as above. Due to their low electrophilicity, competitive 1,2-proton transfer might be faster. Dual-metalcatalyzed carbene sp² C-H functionalization/Conia-ene cascade reactions have also been reported.8 Diazo compounds bearing alkyls have never been used in the above reactions due to their instability and difficulty in separation and purification. N-Tosylhydrazones are safe and easily available precursors of diazo compounds and have attracted considerable attention. Palladium-catalyzed cross-couplings involving N-tosylhydrazones bearing alkyl groups normally give alkenyl products via β -H elimination of the metal alkyl intermediates generated from palladium carbene migratory insertion.^{9a,b} For example, Yamaguchi reported that thioesters reacted with N-tosylhyrazones under Pd-catalysis to furnish Z-alkenyl thioethers (Scheme 1, previous work, 1).¹⁰ Reactions of heteroatom nucleophiles (X-H) with N-tosylhydrazones under transitionmetal free conditions could lead to X-H insertion products. For example, thiophenols/mercaptans coupled with N-tosylhydrazones under basic conditions to give S-H insertion products (Scheme 1, previous work, 2).¹¹ Under photoredox conditions, thiophenols/mercaptans and N-tosylhydrazones have been

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Scheme 1. Reactions of Sulfur Reagents with *N*-Tosylhydrazones



reported to form carbanion intermediates, which can then be trapped by CO_2 or aldehydes but cannot be trapped by ketones (Scheme 1, previous work, 3).¹² Our question was

Table 1. Optimization of the Reaction Conditions for 3^a

whether the palladium intermediates containing β -hydrogens, formed via palladium carbine migratory insertion, could be trapped by more challenging esters instead of undergoing β -hydride elimination. To the best of our knowledge, the formation of a second bond at the same carbon of the palladium carbene, which also contains β -hydrogens, via 1,2 addition or 1,2 addition/elimination with electrophiles such as esters has never been explored and accomplished.

We envision expanding the use of N,N-disubstituted thioamides bearing $\alpha_1 \alpha$ -diesters 1 to intermolecular reactions with N-tosylhydrazones 2 (Scheme 1, this work). Under suitable catalytic systems, a base abstracts the α -H of thiocarbonyl of 1 to form thioenolate anion I, which coordinates with the metal of the carbene III derived from N-tosylhydrazone 2 to give the intermediate V, followed by carbene migratory insertion to give VI. The resulting intermediate VI or the anion derived from VI losing metal might then undergo cascade intramolecular 1,2-addition/ elimination with an ester functionality activated by a cocatalyst, selectively delivering polyfunctional thiophen-3(2H)one 3 (Scheme 1, this work). Various undesired pathways exist that could minimize or halt the formation of the desired products. For instance, β -H elimination or protonation of VI vields 4 or 5. N-Tosylhydrazones 2 might also self-condense to form N-H insertion products 6. Thioamides 1 might also react with 2 to transform the C=S bond into a C=C bond, furnishing enamines 7 (Scheme 1, this work, other possible products). Herein, we disclose that N,N-disubstituted thioamides 1 couple with N-tosylhydrazones 2 bearing alkyl substituents under Pd(II) catalysis, 'BuXPhos as the ligand,

| | ↓ COOMe S S | Ae + NNHTs 2a | catalyst/ligand base, additive solvent, T | S S S S S S S S S S S S S S S S S S S | N ^{-N} -S ^{2C} 6a | or or sa main byproduct: | |
|-----------------------|----------------|----------------------|---|---|--|-----------------------------|------------------------|
| entry | catalyst | ligand | base | additive | T (°C) | solvent | yield ^b (%) |
| 1 ^c | $Pd(TFA)_2$ | | NaO ^t Bu ^d | | 90 | MeCN | 23 |
| 2 ^{<i>c</i>} | $Rh_2(OAc)_4$ | | NaO ^t Bu ^d | | 90 | MeCN | <5% |
| 3 ^c | AgTFAtfa) | | NaO ^t Bu ^d | | 90 | MeCN | 9 |
| 4 ^{<i>c</i>} | CuI | | NaO ^t Bu ^d | | 90 | MeCN | 12 |
| 5 [°] | $Pd(TFA)_2$ | BINAP | NaO ^t Bu ^d | | 90 | MeCN | 14 |
| 6 ^c | $Pd(TFA)_2$ | X-Phos | NaO ^t Bu ^d | | 90 | MeCN | 39 |
| 7 ^c | $Pd(TFA)_2$ | X-Phos | NaO ^t Bu ^d | | 100 | MeCN/toluene (1:1) | 45 |
| 8 ^c | $Pd(TFA)_2$ | X-Phos | LiO ^t Bu ^d | | 100 | MeCN/toluene (1:1) | 29 |
| 9 ^c | $Pd(TFA)_2$ | X-Phos | NaH ^d | | 100 | MeCN/toluene (1:1) | 28 |
| 10 ^c | $Pd(TFA)_2$ | X-Phos | NaOSiMe ₃ ^d | | 100 | MeCN/toluene (1:1) | 48 |
| 11 | $Pd(TFA)_2$ | X-Phos | NaO ^t Bu | | 100 | MeCN/toluene (1:1) | 50 |
| 12 | $Pd(TFA)_2$ | X-Phos | NaO ^t Bu | FeCl ₃ | 100 | MeCN/toluene (1:1) | 62 |
| 13 | $Pd(TFA)_2$ | X-Phos | NaO ^t Bu | AlCl ₃ | 100 | MeCN/toluene (1:1) | 54 |
| 14 | $Pd(TFA)_2$ | X-Phos | NaO ^t Bu | $BF_3 \cdot Et_2O$ | 100 | MeCN/toluene (1:1) | 65 |
| 15 | $Pd(TFA)_2$ | ^t BuXPhos | NaO ^t Bu | $BF_3 \cdot Et_2O$ | 100 | MeCN/toluene (1:1) | 70 |
| 16 | $Pd(TFA)_2$ | ^t BuXPhos | NaOSiMe ₃ | BF ₃ ·Et ₂ O | 100 | MeCN/toluene (1:1) | 0 |
| 17 | | ^t BuXPhos | NaO ^t Bu | BF ₃ ·Et ₂ O | 100 | MeCN/toluene (1:1) | 6 |
| 18 | $Pd(TFA)_2$ | ^t BuXPhos | | BF ₃ ·Et ₂ O | 100 | MeCN/toluene (1:1) | 0 |
| 19 | $Pd(TFA)_2$ | | NaO ^t Bu | BF ₃ ·Et ₂ O | 100 | MeCN/toluene (1:1) | 41 |
| 20 | $Pd(TFA)_2$ | ^t BuXPhos | NaO ^t Bu | - | 100 | MeCN/toluene (1:1) | 55 |

^aReaction conditions: **1a** (0.15 mmol), **2a** (0.375 mmol), 10 mol % of catalyst, 20 mol % of ligand, 50 mol % of additive, NaO'Bu (0.6 mmol) reacted in 3 mL of anhydrous solvent for 12 h. ^bIsolated yield. ^c**2a** (0.3 mmol, 2.0 equiv). ^dNaO'Bu (0.3 mmol, 2.0 equiv). X-Phos: 2-(dicyclohexylphosphino)-2',4',6'-tri(isopropyl)biphenyl; 'BuXPhos: 2-di-*tert*-butylphosphino-2',4',6'-tri(isopropyl)biphenyl.

and with $BF_3 \cdot Et_2O$ as the co-catalyst to selectively access polyfunctional thiophen-3(2*H*)-ones with sulfur-containing tetrasubstituted carbon centers in moderate to good yields.

We started our studies with 1a and 2a as model substrates. Selected results are shown in Table 1 (details are provided in the Supporting Information (SI)). Initially, palladium catalysts including Pd(TFA)₂, Pd(OAc)₂, Pd₂(dba)₃, and Pd(PPh₃)₄ were investigated in the reaction of 0.15 mmol of 1a, 2.0 equiv of 2a, and 2.0 equiv of NaO^tBu in the presence of 10 mol % of palladium catalyst in MeCN at 90 °C under N₂ (Table 1, entry 1, and SI). $Pd(TFA)_2$ was optimal and afforded the desired product 3a in 23% yield (Table 1, entry 1, and SI). Catalysts based on other metals such as Rh, Ag, and Cu were tried but led to inferior results compared to Pd(TFA)₂ (Table 1, entries 2-4, and SI). Then we attempted to investigate the effect of the ligands under Pd(TFA)₂ during this transformation. 20 mol % of ligand including BINAP, dppp, dppb, Xantphos, PCy₃, PPh₃, or X-Phos was added to the entry 1 conditions (Table 1, entries 5, 6, and SI). It was found that X-Phos was optimal (Table 1, entry 6). Next, different solvents and temperatures were screened. It was found that mixed solvents of MeCN and toluene (1:1) at 100 °C (oil bath temperature) improved the yield of 3a to 45% (Table 1, entry 7) and N-H insertion product 6a (21% yield) was the main byproduct. Evaluation of other bases revealed that only NaOSiMe₃ gave a slightly higher yield of 3a than NaO^tBu (Table 1, entries 8–10, and SI), but further study demonstrated that NaOSiMe₃ was not compatible with Lewis acid additives (SI). We improved NaO^tBu to 4.0 equiv and 2a to 2.5 equiv, leading to 3a in 50% yield with 8a (main byproduct) in 25% yield (Table 1, entry 11). We found that introducing an additive such as $FeCl_3$, AlCl₃, or BF₃·Et₂O to activate the ester functionality (Table 1, entries 12-14) under NaO^tBu to facilitate the desired pathway and BF₃·Et₂O was superior (Table 1, entries 12-14). Finally, ligands including Xantphos, DPEphos, DavePhos, ^tBuXPhos, S-Phos, and RuPhos were screened (Table 1, entry 15, and SI). ^tBuXPhos furnished the desired **3a** in 70% yield (Table 1, entry 15), which was identified as the optimized conditions for 3a. The use of sealing tube under the otherwise same conditions afforded 3a in 71% yield (SI). Decreasing the amounts of catalyst or ligand both led to a decrease in the yield of 3a (SI). Deletion experiments demonstrated that $Pd(TFA)_2$ and NaO^tBu were crucial for this cascade reaction (entries 17 and 18), and ^tBuXPhos and $BF_3 \cdot Et_2O$ improved the reactivity and selectivity for 3a (Table 1, entries 19 and 20).

With the optimized conditions in hand, we investigated the substrate scope of the novel cascade reactions of N.Ndisubstituted thioamides 1 and N-tosylhydrazones 2 (Scheme 2). N-Tosylhydrazones 2 were first investigated. N-Tosylhydrazones 2 bearing para (2b-2g)-, meta (2h-2j)-, or ortho (2k)-electron-withdrawing substituted aryls proceeded smoothly to afford the corresponding products 3b-3k in moderate to good yields. It is important to note that fluoro (2b, 2k), chloro (2c, 2h), bromo (2d, 2i), trifluoromethyl (2e, 2j), ester (2f), and even cyano (2g) were all well tolerated. Fluoro, chloro, and bromo could serve as handles for further elaboration, and trifluoromethyl is a privileged group in medicinal chemistry. The reactivity of 21 bearing electrondonating *p*-methoxy-substituted aryl with 1a was sluggish, but still moderate yields of the desired product 31 could be obtained via slightly improved amounts of the catalyst and the ligand. N-Tosylhydrazone 2m bearing heterocycle 2-thienyl was also tolerated. N-Tosylhydrazone 2n bearing a longer alkyl

Scheme 2. Substrate Scope of the Cascade Reactions^a



^{*a*}Reaction conditions: **1** (0.15 mmol), **2** (0.375 mmol), 10 mol % of Pd(TFA)₂, 20 mol % of 'BuXPhos, 50 mol % of BF₃·Et₂O, NaO'Bu (0.6 mmol) reacted in 3 mL of MeCN and toluene (1:1) for 12 h. ^{*b*}Isolated yield. ^{*c*}1 mmol. ^{*d*}15 mol % of Pd(TFA)₂, 30 mol % of 'BuXPhos. ^{*e*}15 mol % of Pd(OAc)₂, 30 mol % of P(2-furyl)₃, **2** (4.0 equiv), NaO'Bu (5.5 equiv).

was relatively inert, furnishing the desired product in low yield (10%). However, a moderate yield of 37% of **3n** could be obtained by the use of $Pd(OAc)_2/P(2-furyl)_3$ catalytic system with improving amounts of **2n** and the base. It is worth noting that *N*-tosylhydrazones (**2o** and **2p**) bearing two aryls were also compatible in the cascade reaction (**3o** and **3p**). In addition, *N*-tosylhydrazone **2q** bearing a phenyl and an ester as

the safe precursor of methyl phenyldiazoacetate afforded the desired product 3q in 54% yield.

Then we turned our attention to the scope of the substrate 1. As illustrated in Scheme 2, an array of N,N-disubstituted thioamides bearing $\alpha_{,\alpha}$ -diesters 1 could bifunctionalize a single carbon of N-tosylhydrazones 2 smoothly. Thioamides 1 bearing other esters, including ethyl esters (1r), isopropyl esters (1s), and benzyl esters (1t), were compatible (3r-3t). Thioamides 1 with para- or meta-electron-donating and electron-withdrawing substituted aryls on nitrogen both afforded the desired product 3u-3aa in moderate to good vields. Methoxy (1u, 1z), fluoro (1v), chloro (1w, 1aa), trifluoromethyl (1x), and keto (1y) in aryls on nitrogen of 1 were all tolerated. In addition, Thioamides 1 containing other alkyl substitutions on nitrogen, including ethyl (3ab), isopropyl (3ac), n-hexyl (3ad), and 3-methoxypropyl (3ae), were all well tolerated, smoothly delivering the corresponding products 3ab-3ae in moderate to good yields.

A one-pot reaction from 2.5 equiv of acetophenone, 2,5 equiv of 4-methylbenzenesulfonohydrazide (which form 2a followed by the removal of solvent), and 1.0 equiv of 1a worked to afford 3a in 61% yield (Scheme 3, a). Derivatization





of the products was investigated. Product **3a** was reduced by $NaBH_4$ to furnish **9a** and **9a'** in 53% total yield with 4:1 diastereoselectivity, and the stereochemistry was assigned using 1D NOESY spectra of **9a** and **9a'** (Scheme 3 (b, 1) and SI). Product **3a** reacted with 1.2 equiv of EtMgBr and 2.0 equiv of MeLi under -78 °C, and only the ester group in **3a** was transformed into ketone to furnish **10a** in moderate yield (Scheme 3 (b, 2)). As mentioned above, the reaction is compatible with halogen atoms which can be used as handles for functionalization. Product **3d** reacted with phenylboronic acid under the reaction conditions reported by Buchwald¹³ to afford **11a** in 87% yield (Scheme 3 (b, 3)). In addition, some chiral ligands instead of 'BuXPhos were investigated, but none

of the enantioselective product 3a was obtained (see the details in the SI). Thus, the anions VII (Scheme 4) are more likely to be the trapped intermediates in this cascade process.

Scheme 4. Proposed Mechanism



A plausible mechanism for this novel reaction is proposed in Scheme 4. NaO^tBu abstracts the α -H of thiocarbonyl of 1 to form the thioenolate anion I, which might coordinate with the palladium catalyst to give the palladium complex IV. The complex IV and the diazo compound II derived from Ntosylhydrazone 2 under NaO^tBu might form the palladium carbene V, which undergoes carbene migratory insertion to give the intermediate VI. The organopalladium moiety in VI attacks the intramolecular ester activated by BF₃·Et₂O to afford product 3. Also, intermediate VI might produce the anion VII along with recovery of $Pd(TFA)_2/^tBuXPhos$, and then the anion VII attacks the intramolecular ester activated by BF₃. Et_2O to afford the product 3 via addition/elimination. Alternatively, $Pd(TFA)_2/^tBuXPhos$ reacts with the diazo compound II derived from N-tosylhydrazone 2 to give the metal carbene intermediate III. Then the thioenolate anion I derived from 1 might undergo ligand exchange with III to give the intermediate V, which forms VI via carbene migratory insertion followed by the similar intramolecular cyclization as above to afford 3. In addition, the thioenolate anion I directly attacks the carbon of III also might form the intermediate VI, and then the intermediate VI directly or the anion VII derived from VI undergoes cyclization to furnish 3.

In conclusion, N,N-disubstituted thioamides bearing $\alpha_1\alpha_2$ diesters coupled with N-tosylhydrazones bearing alkyls with Pd(TFA)₂ as the catalyst, ^tBuXPhos as the ligand, and NaO^tBu as the base at 100 °C and the formed intermediates were unprecedentedly trapped by intramolecular ester functionalities activated by co-catalyst BF3·Et2O, affording polyfunctional thiophen-3(2H)-ones with sulfur-containing tetrasubstituted carbon centers in moderate to good yields. This represents the first time that the formed organopalladium intermediates containing β -hydrogen from palladium carbene migratory insertion selectively form the second bond at the same carbon via 1,2-addition/elimination with esters instead of undergoing β -hydrogen eliminations. The novel cascade reaction utilizes odorless, nontoxic, safe, and easily available starting materials. Wide substrate scope and a broad range of functional groups are tolerated. Products possess rich and valuable structures in medicinal chemistry and materials. Developing other novel reactions to selectively construct

multiple bonds in a single process with odorless and nontoxic sulfur reagents as well as evaluation of the biological activities of novel thiophen-3(2H)-ones are currently being investigated in our laboratory and in our cooperative laboratory.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03796.

Experimental procedures and spectroscopic characterization data, ¹ H and ¹³C NMR spectra of the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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