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Pd-catalyzed oxidative coupling of monosubstituted sydnones and terminal alkynes

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ABSTRACT

The Pd-catalyzed oxidative coupling of N-substituted sydnones and terminal alkynes offers a quick, one-step synthesis of 4-alkynylsydnones in moderate to good yields.

Sydnone[1] belongs to a class of heterocycles typically referred to as mesoionic rings (Fig. 1).[2] Structurally sydnone has a 5-membered oxadiazole skeleton exhibiting aromaticity through a net separation of formal positive and negative charges. Since its discovery in 1935,[3] sydnone has attracted significant attention from a wide variety of research areas due to its interesting structure and physicochemical properties. Sydnone derivatives have been recognized to exhibit a spectrum of bioactivities, including antibacterial,[4] anticancer,[5] anti-inflammatory,[6] and antimalarial.[7] Chemically, sydnone exhibits reactivity typical of arenes, specifically electrophilic aromatic substitution, including halogenation[8] and acylation[9] reactions. Recently, the chemistry of sydnones has been more focused on its reactivity as a cyclic 1,3-dipole in [3+2] cycloaddition reactions with alkynes to afford pyrazoles.[10] Their further development requires improved methods for the preparation of sydnones.

Traditionally, sydnones are prepared from N-substituted amino acids by an N-nitrosation/cyclodehydration sequence.[11] This procedure is still the most widely used preparation today, with different modifications available.[12] However, this method is limited to amino acids that are readily available. In an ongoing investigation in our two groups of aryne dipolar cycloaddition chemistry using sydnones as the 1,3-dipole,[13] we needed to prepare a variety of sydnones bearing diverse substitution patterns. Unfortunately, for many substituted sydnones, particularly 4-vinyl and 4-alkynyl sydnones, the amino acid route is simply not viable, and alternative routes are needed.

In this regard, Moran et al. developed a Pd-catalyzed cross-coupling reaction of N-substituted sydnones with vinylic/aryl halides,[14] leading to an easy and efficient synthesis of 4-vinylic and 4-arylsydnones. However, in that report, there was only one example using a 1-bromoalkyne as the electrophile to prepare 4-alkynylsydnones and the yield was only modest (Eq. 1).[14b] Besides this protocol, there are only two general approaches available for the preparation of 4-alkynylsydnones. One method developed by Kalinin et al. (Eq. 2)[15] involves the BuLi deprotonation of N-substituted sydnones, a low-temperature transmetallation to Cu(I),[16] followed by a Sonogashira coupling with 1-bromo-2-(trimethylsilyl)acetylene, which has to be prepared. A subsequent removal of the TMS group and finally another Sonogashira coupling with a halide are required to complete the synthesis. The other method developed by Turnbull et al. (Eq. 3)[17] involves a Sonogashira coupling of 4-bromosydnone with a terminal alkyne. Unfortunately, neither of these methods seems attractive as the former consists

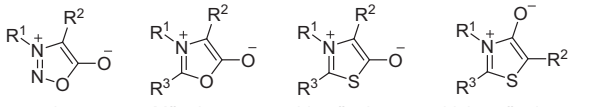

Figure 1. Sydnone and other mesoionic rings.

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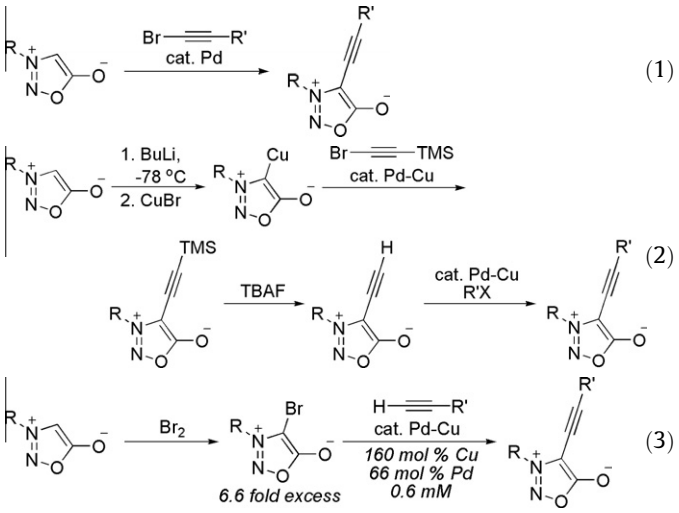
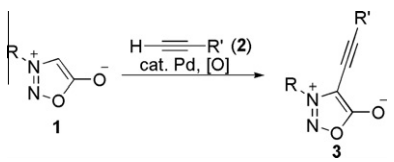
of a multi-step synthesis, and the latter calls for the use of near stoichiometric amounts of metal catalysts, a 6.6-fold excess of 4-bromosydnone, which was prepared through a multi-step synthesis, and an extreme dilution (0.15 mmol scale in 250 mL of Et_3N as the solvent). Given this situation, there remains a lack of an efficient, operationally friendly method to prepare 4-alkynylsydnones.



Recently a variety of Pd-catalyzed oxidative coupling reactions have been developed,[18,19] among which terminal alkynes can be used as the nucleophilic coupling partner.[19] Such success encouraged us to investigate the feasibility of reacting N-substituted sydnones directly with terminal alkynes under Pd-catalyzed conditions employing a terminal oxidant (Scheme 1). Ideally, this approach would offer the easiest way to synthesize 4-alkynylsydnones.

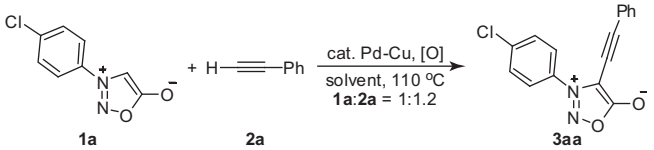
With this in mind, we first investigated the reaction of *N*-(4-chlorophenyl)sydnone (**1a**) with phenylacetylene (**2a**) in refluxing toluene (Table 1), using 5 mol % $Pd(OAc)_2$ as the catalyst in combination with 10 mol % $CuCl_2$ to help regenerate Pd(II), and 2.0 equiv of Ag_2O as the terminal oxidant. The reaction successfully afforded the oxidatively coupled product **3aa** in a 48% yield (entry 1). Although $CuCl_2$ can be replaced by $Cu(OAc)_2$ without significantly affecting the yield (entry 2), replacing $Pd(OAc)_2$ with $PdCl_2$ (entry 3), or Ag_2O with Ag_2CO_3 (entry 4), or toluene with DMF (entry 5) led to complete failure of the reaction. Somewhat surprisingly, although theoretically Ag_2O can serve as the oxidant, it is critical to run the reaction in air (open flask). Running the reaction under nitrogen failed to work (entry 6), and replacing Ag_2O with a stoichiometric quantity of Cu(II) also afforded only a trace of the desired alkynylsydnone (entry 7). Use of less than 2 equiv of Ag_2O afforded a comparable yield (entry 8), but was less favorable due to the long reaction time and lower conversion.

With these conditions optimized, we screened other substrates. To our surprise, we soon realized that these 'optimized' reaction conditions did not work for other substrates. In those reactions, oxidative dimerization of the terminal alkyne was the major, sometimes exclusive, event. Therefore, further optimization was needed. We hypothesized that alkyne **2** should be added slowly



Scheme 1. Oxidative coupling of sydnone and an alkyne.

Table 1
Reaction optimization[a]



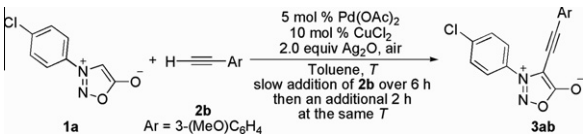
Entry	Pd (5 mol %)	Cu (mol %)	Oxidant (equiv)	Solvent	*t* (h)	Yield[b] (%)
1	$Pd(OAc)_2$	$CuCl_2$ (10)	Ag_2O (2.0)	Toluene	18	48
2	$Pd(OAc)_2$	$Cu(OAc)_2$ (10)	Ag_2O (2.0)	Toluene	18	44
3	$PdCl_2$	$CuCl_2$ (10)	Ag_2O (2.0)	Toluene	24	0
4	$Pd(OAc)_2$	$CuCl_2$ (10)	Ag_2CO_3 (2.0)	Toluene	24	Trace
5	$Pd(OAc)_2$	$CuCl_2$ (10)	Ag_2O (2.0)	DMF	24	0
6	$Pd(OAc)_2$	$CuCl_2$ (10)	Ag_2O (2.0)	Toluene	18	Trace[c]
7	$Pd(OAc)_2$	$CuCl_2$ (200)	None	Toluene	18	Trace
8	$Pd(OAc)_2$	$CuCl_2$ (10)	Ag_2O (1.2)	Toluene	24	44

[a] Reaction conditions: 0.4 mmol scale, 5 mL of solvent.
[b] Isolated yield.
[c] Reaction was carried out under N_2.

in portions, or more ideally with a syringe pump to reduce its concentration and therefore reduce homocoupling of the alkyne. Thus, we added alkyne **2b**, which did not work under the optimized conditions shown in Table 1, entry 1, in six portions over 6 h, only to find that the coupling failed again (Table 2, entry 1). Nonetheless, lowering the temperature to 90 °C led to a modest yield of 25% (entry 2). The optimal temperature proved to be 75 °C (entry 3). We realized, by TLC analysis, that the reaction seriously slowed down toward the end, presumably because the Ag mirror formed in the reaction may help Pd(0) deposit and therefore lose its activity. Thus, the slow addition of another 5 mol % of the Pd catalyst together with 1.5 equiv of **2b** via syringe pump was performed, resulting in the best yield of 73% so far obtained (entry 5). It should be pointed out that although this operation is still a bit awkward, these reaction conditions are much improved when compared with those in Eqs. 2 and 3.[20]

We then screened these newly optimized conditions against a variety of sydnones and alkynes (Table 3). Different sydnones were first investigated (entries 1–7). As can be seen, most *N*-aryl sydnones reacted well, affording the desired products in good yields, except for *N*-(4-nitrophenyl)sydnone (entry 6). Even an aryl bromide can be tolerated (entry 5). However, an *N*-methyl variant proceeded much less smoothly (entry 7).[21] For alkynes, it was

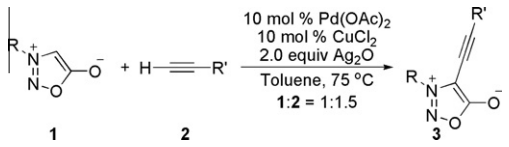
Table 2
Second-round optimization[a]



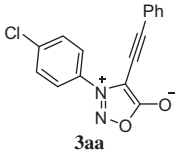
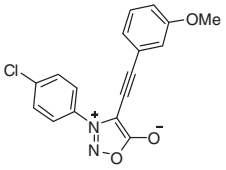
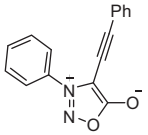
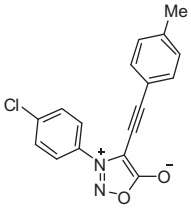
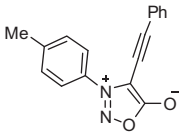
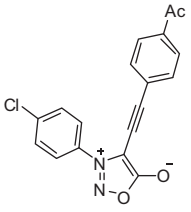
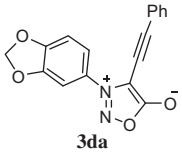
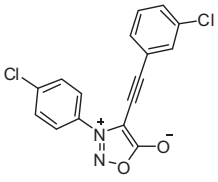
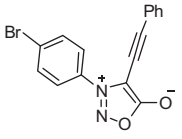
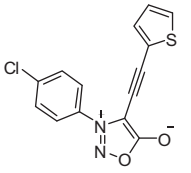
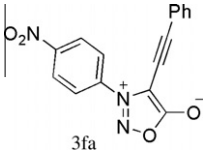
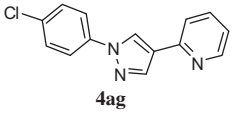
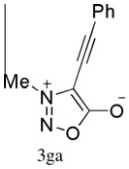
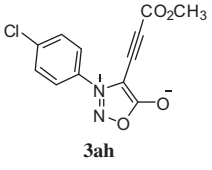
Entry	Addition of **2b**	*T* (°C)	Yield[b] (%)
1	Portionwise, 0.2 equiv/h	110	Trace
2	Portionwise, 0.2 equiv/h	90	25
3	Portionwise, 0.2 equiv/h	75	50
4	Portionwise, 0.2 equiv/h	60	45
5[c]	Via syringe pump	75	73

[a] Reaction conditions: 0.4 mmol scale, 5 mL of toluene (half in the flask, half to dissolve **2b**).
[b] Isolated yield.
[c] 1.5 equiv of **2b** and another 5 mol % Pd in 2.5 mL of toluene.

Table 3
Reaction scope[a]



1 2 3

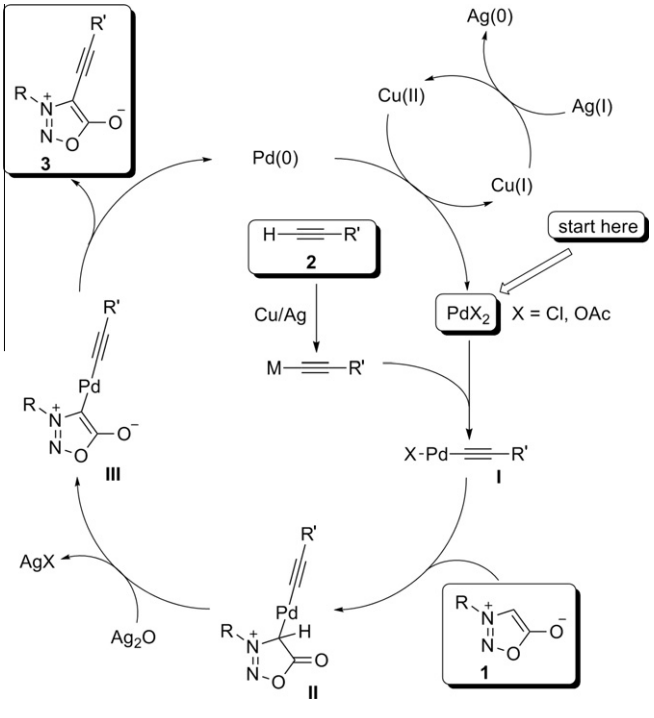
Entry	R	R′	Product	Yield[b] (%)	Entry	R	R′	Product	Yield[b] (%)
1	4-ClC_6H_4 (**1a**)	Ph (**2a**)	 **3aa**	69	8	4-ClC_6H_4 (**1a**)	3-$(MeO)C_6H_4$ (**2b**)	 **3ab**	73
2	Ph (**1b**)	Ph (**2a**)	 **3ba**	72	9	4-ClC_6H_4 (**1a**)	4-MeC_6H_4 (**2c**)	 **3ac**	78
3	4-MeC_6H_4 (**1c**)	Ph (**2a**)	 **3ca**	69	10	4-ClC_6H_4 (**1a**)	4-AcC_6H_4 (**2d**)	 **3ad**	76
4	3,4-$(OCH_2O)C_6H_4$ (**1d**)	Ph (**2a**)	 **3da**	72	11	4-ClC_6H_4 (**1a**)	3-ClC_6H_4 (**2e**)	 **3ae**	66
5	4-BrC_6H_4 (**1e**)	Ph (**2a**)	 **3ea**	60	12	4-ClC_6H_4 (**1a**)	2-Thiophenyl (**2f**)	 **3af**	38[c]
6	4-$(O_2N)C_6H_4$ (**1f**)	Ph (**2a**)	 3fa	0	13	4-ClC_6H_4 (**1a**)	2-Pyridyl (**2g**)	 **4ag**	25[d]
7	Me (**1g**)	Ph (**2a**)	 3ga	29	14	4-ClC_6H_4 (**1a**)	CO_2Me (**2h**)	 **3ah**	33

[a] All reactions are carried out on a 0.4 mmol scale.
[b] Isolated yields.
[c] Incomplete conversion, 37% of **1a** was recovered.
[d] The [3+2] cycloaddition was not observed under the same conditions in the absence of Pd, Cu, and Ag.

observed that substituted phenylacetylenes worked best (entries 8–11), with either an electron-donating group (entry 8) or an electron-withdrawing group (entry 10) tolerated. Heterocyclic acetylenes reacted much more slowly and gave substantially lower conversions to alkynylsydnones (entries 12 and 13). For example, 2-ethynylthiophene (**2f**) only gave a 38% yield of the desired product, with 37% of **1a** recovered (entry 12). 2-Ethynyl pyridine on the other hand afforded a product apparently arising by a [3+2] cycloaddition, followed by elimination of CO_2 (entry 13). Interestingly, this process seemed to be promoted by the metal catalysts present in the reaction mixture as no such cycloaddition was observed in the absence of Pd, Cu, and Ag. Alkyl-substituted alkynes unfortunately did not work well. While methyl propiolate (**2h**) gave a low conversion of the sydnone and only a 33% yield, no other such alkynes worked, including heptyne, *N*-(3-butynyl)phthalimide, 1-ethynylcyclohexanol, and homopropargyl alcohol. Thus, the scope of the current reaction is limited to arylacetylenes. Literature preparations by Kalinin and Turnbull are in agreement with this observation as they are also limited to acetylenes with sp^2 bonded carbon substitutents.[15–17] It should be noted that Kalinin's method is capable of preparing the desired product of **1b** and **2g** in a low yield, while our method could not.

The putative mechanism of this reaction is straightforward (Scheme 2). Starting with Pd(II), transmetallation with a presumed copper or silver acetylide generates an alkynyl Pd species (**I**). Coordination of the sydnone (**1**) to the Pd center generates a cationic species (**II**). Subsequent loss of the acidic proton at C4 results in the formation of a 4-palladiosydnone (**III**), which reductively eliminates the desired product **3** and affords Pd(0). The Cu and Ag salts regenerate Pd(II) from Pd(0) to complete the cycle. Although this mechanism explains the product formation, it should be considered as a simplified version, since the precise involvement of air[22,23] and the regeneration of Pd(II) from Pd(0) remain elusive.

In conclusion, we have developed a straightforward synthesis of 4-alkynylsydnones from terminal alkynes under Pd-catalyzed oxidative coupling conditions. Although this reaction still requires the slow addition of alkynes and the scope of the alkynes is still limited, it is much more operationally friendly than previous methods.



Scheme 2. Putative mechanism (simplified).

Acknowledgments

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20. Representative procedure (Table 3, entry 1): To an oven-dried 10 mL round-bottom flask equipped with a stirrer bar was added 79 mg of **1a** (0.4 mmol), followed by 4.8 mg of $Pd(OAc)_2$ (0.021 mmol, 5 mol %), 6.0 mg of $CuCl_2$ (0.045 mmol, 11 mol %), and 186 mg of Ag_2O (0.8 mmol, 2.0 equiv). Toluene (2.5 mL) was added and the mixture was stirred at 75 °C while open to air. To this flask was added a solution containing 62 mg of **2a** (0.6 mmol, 1.5 equiv) and another 4.8 mg of $Pd(OAc)_2$ (0.021 mmol, 5 mol %) in 2.5 mL of toluene via syringe pump over 6 h. After complete addition, the reaction was continued for 2 h and judged complete by TLC. The mixture was then cooled to ambient temperature, filtered, and washed with EtOAc. The filtrate was washed once with brine and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc = 4:1), to afford 81 mg of **3aa** (69%) as a brown solid; mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H), 7.67-7.61 (m, 2 H), 7.44-7.31 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 138.9, 132.7, 131.3, 130.2, 129.6, 128.5, 124.8, 121.1, 103.4, 95.4, 72.8; HRMS (ESI) calcd for $C_{17}H_{12}ClN_2O_3$ (M+H) 297.0425, found 297.0422.
21. An *N*-benzyl variant was also attempted. It resulted in a mixture containing the desired product, but we were not able to purify the product.
22. For reports of the mechanistic details of aerobatic oxidation of Pd(0) to Pd(II), see: (a) Konnick, M. M.; Decharin, N.; Popp, B. V.; Stahl, S. S. *Chem. Sci.* **2011**, *2*, 326; (b) Popp, B. V.; Stahl, S. S. *Chem. Eur. J.* **2009**, *15*, 2915; (c) Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 5753.
23. It should be noted that Moran's cross-coupling reactions were also carried out in air. See Ref.[14]