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Copper(I)-Catalyzed Cycloaddition of 4-Bromosydnones and Alkynes for the Regioselective Synthesis of 1,4,5-Trisubstituted Pyrazoles

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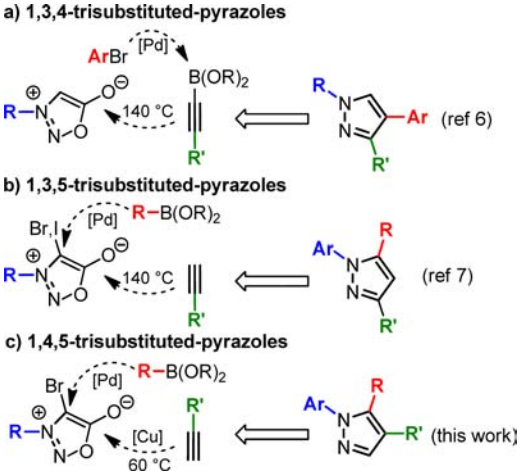
Supporting Information

ABSTRACT: Copper-catalyzed cycloaddition of alkynes with 4-bromosydnones provides a convenient, mild, and regioselective method for the synthesis of a wide range of bromopyrazoles. The broad functional group tolerance of the cycloaddition reaction and further palladium-catalyzed cross-coupling reactions allowed the preparation of polyfunctionalized 1,4,5-pyrazoles that are otherwise difficult to obtain by conventional methods.

Pyrazoles represent a central heterocyclic building block largely employed both by the pharmaceutical[1] and the agrochemical[2] industries for the design and synthesis of biologically active compounds. *N*-Aryl-polysubstituted pyrazoles are more particularly present in several FDA-approved pharmaceutical drugs such as celecoxib (Celebrex), apixaban (Eliquis), and rimonabant (Acomplia). As a consequence, a number of efficient synthetic routes to pyrazoles have been developed.[3] Among them, the thermal 1,3-dipolar cycloaddition reaction of sydnones and alkynes appeared as a promising approach to construct polysubstituted pyrazoles.[4] Sydnones are stable mesoionic compounds that can react as azomethine imine-type dipoles with electron-deficient alkynes at elevated temperatures, giving rise to pyrazoles by CO_2 extrusion.[5] Harsh conditions and low regioselectivity have long limited the interest of this thermal cycloaddition, but some nice examples of its usefulness for trisubstituted pyrazole synthesis appeared in the last years. Harrity and co-workers have notably showed that alkynylboronates undergo cycloaddition reactions with sydnones in a good regiocontrolled manner leading to 1,3,4-trisubstitued pyrazole boronic esters, further employed in cross-coupling Pd-catalyzed reactions (Scheme 1a).[6] Several methods leading to 1,3,5-trisubstitued pyrazoles from 4-halogenosydnones were also developed (Scheme 1b).[7] However, these cycloaddition procedures require elevated temperatures, therefore preventing their use on sensitive substrates, and cannot provide 1,4,5-trisubstituted pyrazoles for which no general and regiocontrolled synthetic route is available to date.

Recently, our group has developed a copper(I)-catalyzed cycloaddition reaction of sydnones with terminal alkynes (CuSAC)[8] which presents similarities with the well-known copper(I)-catalyzed azide−alkyne cycloaddition reaction (CuAAC).[9] The positive effects of copper catalysis on the reaction of sydnones with alkynes are numerous: yields are usually very high, regioselectivity is total and opposite to the thermal mode, tolerance to chemical and biological functional groups is almost perfect, and reaction conditions are simple and mild (organic or aqueous solvents, temperatures from 30 to 60 °C). However, the CuSAC reaction is actually limited to the synthesis of 1,4-disubstitued pyrazoles. To address this deficiency, we were interested in exploring the impact of substitutions in position 4 of the sydnone mesoionic ring on the CuSAC reaction with the final goal of providing the first general route to 1,4,5-trisubstituted pyrazoles (Scheme 1c). Indeed, halogenation on position C-4 of sydnones is easy,[10] therefore offering possible functionalization before or after the cyclization step by Pd-catalyzed-coupling reactions.

Scheme 1. Sydnone Approaches to Trisubstituted Pyrazoles



A series of C-4-substituted sydnones **1** were therefore synthesized and reacted with phenylbutyne **2** under standard CuSAC conditions (Table 1). The results indicated that substitution at position 4 was globally highly prejudicial to the reaction, with only the presence of a methyl group dropping the yield to 7% (compare entries 1 and 2 in Table 1). Unfortunately, 4-iodosydnones were found to be unstable

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Table 1. Influence of C-4 Substitution of Sydnones on the CuSAC Reaction[a]

entry	R	yield of **3**[b] (%)	**3**/**4**
1	H	98	100/0
2	Me	7	100/0
3	Ph	no reaction	
4	CF_3	no reaction	
5	CN	10	50/50
6	CHO	no reaction	
7	Cl	80	96/04
8	Br	74	83/17
9	I	traces	

[a]Experiments were carried at 0.1 M with 1 equiv of reactants, 1 equiv of triethanolamine, 20 mol % of $CuSO_4$-bathophenanthroline disulfonate (**L2**) complex, and 2 equiv of sodium ascorbate. [b]isolated yields.

under the reaction conditions and undergo fast deiodination, but 4-chloro- and 4-bromosydnones successfully participated in the CuSAC reaction although regiocontrol was partially lost (entries 7 and 8, Table 1).

This finding suggests that 1,4,5-trisubstituted pyrazoles may be obtained through CuSAC reaction with 4-bromosydnones and further postcyclization functionalization by Pd-catalyzed coupling reactions. We thus focused our efforts on the optimization of the reaction with bromosydnones with the objective of increasing the regioselectivity of the cycloaddition. We first screened a series of ligands known to modulate the Cu(I) catalytic activity in the CuAAC reaction.[11] Contrary to what was observed for the CuAAC reaction, tristriazole ligands **L4**, **L5**, and **L8** and trisbenzimidazole ligands **L6** and **L7** were found to be surprisingly less efficient than bathophenanthroline **L2** (compare entry 4 with entries 7, 9, and 11−13 in Table 2), suggesting that bidentate ligands form more active copper complexes for CuSAC than tridentate ones. Increasing the temperature to 100 °C was also prejudicial to the reaction efficiency and induced the formation of the debrominated byproduct **5** (compare entries 5, 8, and 10 with 4, 7, and 9 in Table 2). We were then interested in testing diimidazoquinoxalines **L9**−**L12** as new ligands for copper catalysis. These compounds were described in only two papers for their optical properties[12] but were never used as ligands for catalysis. We were particularly interested in seeing if the higher angle between the two coordinative nitrogen atoms, as compared to phenanthrolines, may have an impact on the catalytic performances of the corresponding copper complexes. To our delight, the assays confirmed the anticipated beneficial effect of these ligands on the reaction (entries 14−17, Table 2). Although yields and reaction times were only slightly increased, the main positive effect was observed on the regioselectivity of the cycloaddition. **L11** emerged as the optimum ligand leading to 5-bromopyrazole **3** as the exclusive product in a good yield (entry 16, Table 1) and was therefore selected for further investigations. The ligand effect on this reaction is rather spectacular: no trace of pyrazole product was observed under ligand-free conditions (entry 1, Table 2).

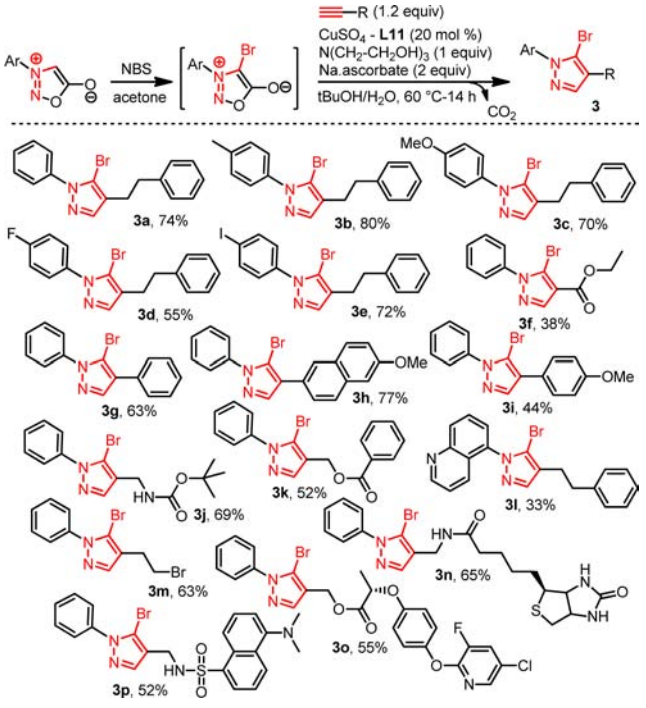
Table 2. Optimization of the Reaction Conditions[a]

entry	ligand	temp (°C)	yield of **3**[b] (%)	**3**/**4**/**5**[c]
1	none	100	n.d.[d]	
2	L1	60	67	83/10/07
3	L2	25	54	84/16/0
4	L2	60	74	83/17/0
5	L2	100	42	36/03/61
6	L3	100	n.d.	
7	L4	60	16	97/03/0
8	L4	100	65	86/03/11
9	L5	60	32	92/08/0
10	L5	100	45	78/06/16
11	L6	100	n.d.	
12	L7	100	n.d.	
13	L8	100	27	97/0/03
14	L9	60	60	97/0/03
15	L10	60	13	100/0/0
16	**L11**	**60**	**75**	**100/0/0**
17	L12	60	74	100/0/0

[a]Experiments were carried at 0.1 M with 1 equiv of reactants. [b]Isolated yields. [c]Ratios determined by ^{1}H NMR and HPLC. [d]62% yield of debrominated **1** was isolated.

With these optimized conditions in hand, we investigated the scope of the reaction. To simplify the procedure, a one-pot protocol from sydnones was used to generate 5-bromopyrazoles. Bromosydnones were first prepared quantitatively by electrophilic bromination with *N*-bromosuccinimide and used directly without purification in the CuSAC reaction. This protocol was found to be remarkably tolerant to all tested functional groups either present on the sydnone or the alkyne substrates (Scheme 2). Yields were globally good, although low conversions of the bromosydnone substrates **3f**, **3i**, and **3l** were observed. In all cases, crude reactions were clean, with no traces of regioisomer or debromination byproducts.

Scheme 2. Scope of the Reaction (Isolated Yields)



We then tried to extend this approach to the preparation of 1,4,5-trisubstitued pyrazoles by using the formed 5-bromopyrazoles in Pd-catalyzed cross-coupling reactions with appropriate boronic acids. As with many *N*-heterocyclic substrates, pyrazoles have the reputation of being poor substrates for the

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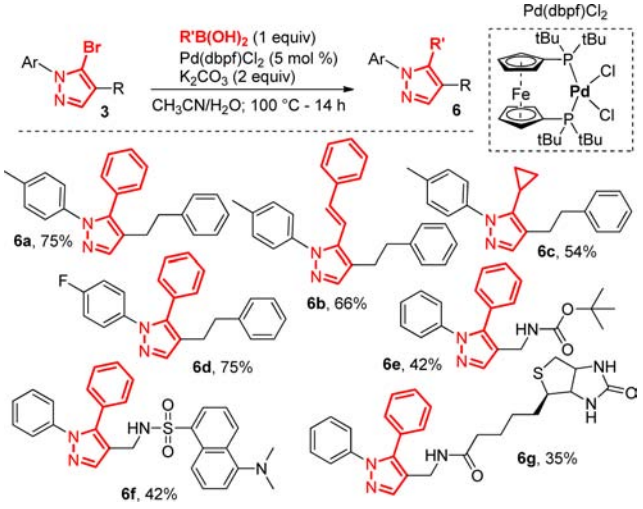
Suzuki reaction.[13] To our knowledge, no Suzuki coupling on *N*-aryl-5-bromopyrazole **3** has been described so far in the literature. We thus performed a screening of a series of Pd sources (Table S1, Supporting Information) and identified 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (Pd(dbpf)Cl_2)[14] as the most efficient catalyst (Scheme 3). With

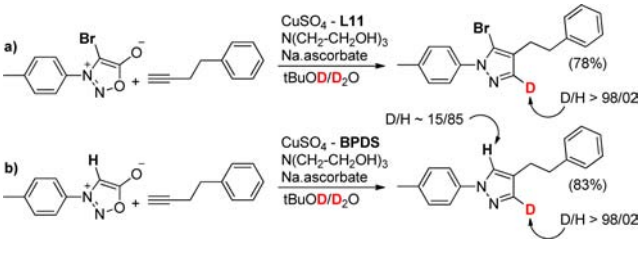
Scheme 3. Preparation of 1,4,5-Pyrazoles 6



this catalyst, aryl-, styryl-, and alkylboronates proceeded smoothly in Suzuki coupling with 5-bromopyrazole **3b**, and the procedure was found to be compatible with the more functionalized bromopyrazoles **3j**, **3p**, and **3n**.

Sydnones are known to share common features with *N*-heterocyclic carbenes[15] and to form stable complexes with transition metals,[16] including copper,[17] by forming a carbon−metal bond in position 4 of the mesoionic ring under basic conditions. The fact that 4-methyl-, 4-chloro-, and 4-bromosydnones are substrates for the CuSAC reaction (see Table 1) does not account for a carbene-like process. The mechanism is more likely to proceed through coordination of the nitrogen atom in position 2 of sydnones by classical copper(I) acetylide species. Furthermore, when the reaction is performed in deuterated solvent, labeling occurs in position 3 of the pyrazole ring (Scheme 4) starting both from sydnone or

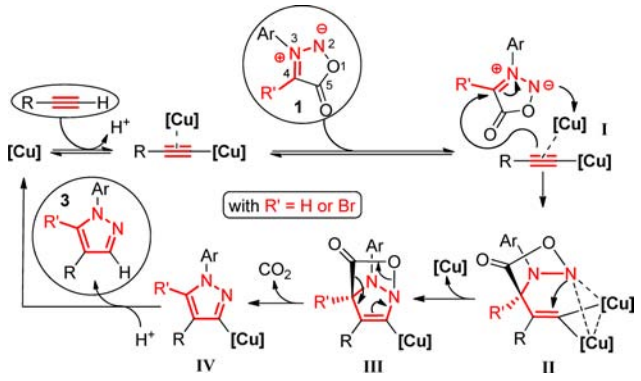
Scheme 4. Mechanistic Investigation



bromosydnone, which is in agreement with deprotonation of the starting alkyne by copper and deuterolysis of the carbon−copper bond of a 3-cuprated pyrazole intermediate.

Based on these experiments and on the established mechanism of the CuAAC reaction,[18] we suggest the mechanistic proposal outlined in Scheme 5. First, the in situ formed copper−acetylide species **I** reversibly coordinates the N-2 atom of the dipolar resonance form **1** of the sydnone,

Scheme 5. Proposed Mechanism



provoking nucleophilic attack at C-4 by the *β*-carbon of the acetylide to form intermediate **II**. This step creates a covalent C−C bond and is highly sensitive to both steric and electronic effects of the R′ substituent as illustrated by the results in Table 1. Bulky moieties or electron-withdrawing groups, which decrease the nucleophilicity of N-2, are prejudicial to the reaction. Ring closure and decarboxylative retro-Diels−Alder reaction then afford pyrozolide **IV**. Protonolysis then completes the cycle, liberating pyrazole **3** and regenerating the copper catalyst.

In conclusion, we described a stepwise copper and palladium-catalyzed route to 1,4,5-trisubstitued pyrazoles. This synthetic approach is the first to permit complete control over the placement of substituents in positions 1, 4, and 5 of the pyrazole core and therefore would be a valuable addition to known pyrazole construction approaches and would aid the search for new bioactive pyrazoles. The copper-catalyzed cycloaddition reaction of bromosydnones with alkynes, which display high functional group compatibility and excellent chemo- and regioselectivities, is the key step of the process. Imidazoquinoxalines have been used for the first time as new bidentate ligands for copper catalysis and proved to be highly beneficial to the CuSAC reaction. We think these compounds may find broad applications as transition-metal ligands in the future.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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