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A palladium-catalyzed reaction of aryl halides, potassium metabisulfite, and hydrazines†

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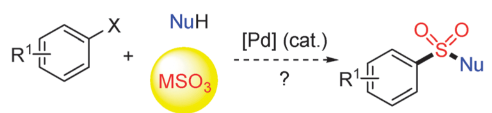
Aryl *N*-aminosulfonamides could be easily produced *via* a palladium-catalyzed coupling of aryl halides, potassium metabisulfite, and hydrazines. Potassium metabisulfite is an excellent equivalent of sulfur dioxide in the reaction of palladium-catalyzed aminosulfonylation.

Significant efforts continue to be underway for the applications of sulfur dioxide in organic synthesis, due to the enormous scale of annual production.[1] Although using sulfur dioxide as a reagent or a coordination partner has been demonstrated in several organic transformations,[2–4] applications of sulfur dioxide in organic synthesis are restricted, presumably due to the handling problem associated with this toxic gaseous reagent.[5] Recently, there has been a breakthrough by using DABCO–bis(sulfur dioxide) as the source of sulfur dioxide in several organic reactions, as reported by Willis and co-workers.[6] This bench-stable solid overcomes the defects of gaseous sulfur dioxide as mentioned above.[6,7] However, the scope of the reported process is limited. For example, only aryl/vinyl iodide could be utilized in the palladium-catalyzed coupling reactions. Additionally, the preparation of DABCO–bis(sulfur dioxide) is difficult, which is an energy consuming process.[6] Moreover, an excess amount of DABCO has to be which is wasteful.

It is well known that there are many sulfites in Nature, which are formed directly by absorption of the gaseous sulfur dioxide from air. It would be highly desirable and attractive for incorporation of sulfonyl groups into organic molecules if the inorganic sulfites could serve as the source of sulfur dioxide in organic transformations, especially in transition metal catalyzed reactions (Scheme 1). This environmentally benign process would open a new avenue for the synthesis of sulfonyl derivatives. Herein, we report the first example of using potassium metabisulfite as a sulfur dioxide equivalent in the reaction of palladium-catalyzed aminosulfonylation under mild conditions. Not only aryl iodides but also aryl bromides are workable during the reaction process.



Scheme 1 Proposed synthetic route to sulfonyl derivatives *via* a palladium-catalyzed reaction of aryl halides, sulfite, with nucleophiles.

Our initial studies were performed for a model reaction of 1-iodo-4-methylbenzene **1a**, sodium hydrogensulfite, with morpholin-4-amine **2a** (Table 1). The reaction was catalyzed by palladium acetate (5 mol%) with $P^tBu_3{\cdot}HBF_4$ (10 mol%) in the presence of TBAB (tetrabutylammonium bromide) in DMF at 80 °C (Table 1, entry 1). We envisioned that the presence of TBAB would act as a base as well as a phase transfer reagent in the reaction.[7] However, only a trace amount of product was detected. The result was not improved when the solvent was changed to MeCN (Table 1, entry 2). Gratifyingly, the desired 4-methyl-*N*-morpholinobenzenesulfonamide **3a** was isolated in 11% yield when the reaction occurred in toluene (Table 1, entry 3). Further screening of solvents revealed that the reaction worked efficiently in 1,4-dioxane, which afforded the product in 21% yield (Table 1, entries 4–6). Other inorganic sulfites were examined subsequently. The reactions failed when sodium sulfite, potassium sulfite, or sodium metabisulfite was employed in the reaction as the source of sulfur dioxide (Table 1, entries 7–9). Compound **3a** could be generated in 15% yield when zinc sulfite was used as a replacement (Table 1, entry 10). To our delight, the outcome could be improved when potassium metabisulfite was utilized as a sulfur dioxide equivalent, which furnished the expected product **3a** in 67% yield (Table 1, entry 11). The presence of TBAB is essential, and the yield was decreased to 26% in the absence of TBAB (Table 1, entry 12). Further exploration of the ligand effects led to poor results. No better yields were obtained when various phosphine ligands or *N*-heterocyclic carbene were employed in the reaction (Table 1, entries 13–24). We envisioned that the electron enriched P^tBu_3 would promote the oxidative addition of Pd(0) to aryl halide, and the bulkiness of P^tBu_3 would promote the reductive elimination during the reaction process. The yield was dramatically increased to 98% when 20 mol% of $P^tBu_3{\cdot}HBF_4$ was used in the reaction (Table 1, entry 25). However, the reaction was retarded under lower temperature (Table 1, entries 26 and 27). A comparable yield (97%) was obtained when the reaction

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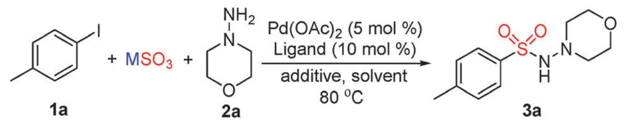
Table 1 Initial studies for the palladium-catalyzed reaction of 1-iodo-4-methylbenzene **1a**, inorganic sulfite, with morpholin-4-amine **2a**[a]



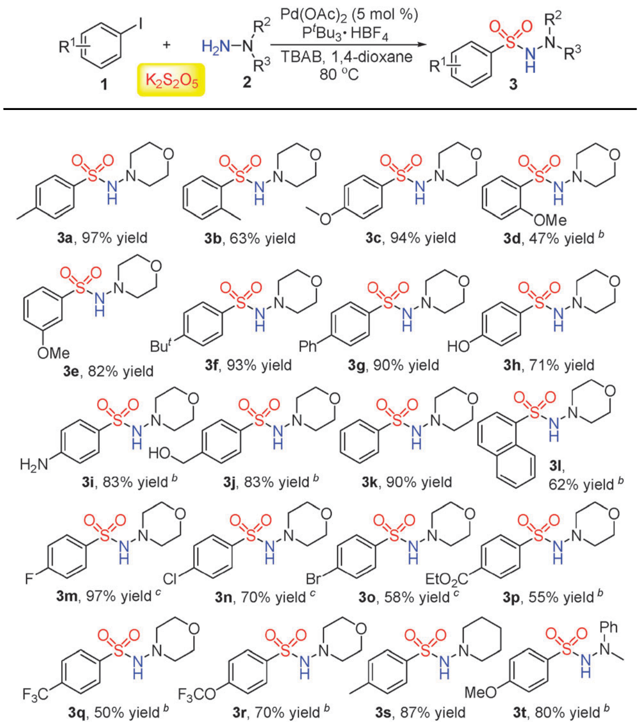
Entry	MSO_3	Ligand	Additive	Solvent	Yield[b] (%)
1	$NaHSO_3$	$P^tBu_3{\cdot}HBF_4$	TBAB	DMF	Trace
2	$NaHSO_3$	$P^tBu_3{\cdot}HBF_4$	TBAB	MeCN	Trace
3	$NaHSO_3$	$P^tBu_3{\cdot}HBF_4$	TBAB	Toluene	11
4	$NaHSO_3$	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	21
5	$NaHSO_3$	$P^tBu_3{\cdot}HBF_4$	TBAB	DCE	10
6	$NaHSO_3$	$P^tBu_3{\cdot}HBF_4$	TBAB	^{t}BuOH	Trace
7	Na_2SO_3	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	Trace
8	K_2SO_3	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	Trace
9	$Na_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	Trace
10	$ZnSO_3$	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	15
11	$K_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	67
12	$K_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	—	1,4-Dioxane	26
13	$K_2S_2O_5$	PCy_3	TBAB	1,4-Dioxane	nr
14	$K_2S_2O_5$	PPh_3	TBAB	1,4-Dioxane	18
15	$K_2S_2O_5$	BINAP	TBAB	1,4-Dioxane	Trace
16	$K_2S_2O_5$	S-Phos	TBAB	1,4-Dioxane	16
17	$K_2S_2O_5$	Xant-Phos	TBAB	1,4-Dioxane	Trace
18	$K_2S_2O_5$	DPPF	TBAB	1,4-Dioxane	Trace
19	$K_2S_2O_5$	John-Phos	TBAB	1,4-Dioxane	Trace
20	$K_2S_2O_5$	X-Phos	TBAB	1,4-Dioxane	Trace
21	$K_2S_2O_5$	DPPP	TBAB	1,4-Dioxane	Trace
22	$K_2S_2O_5$	Ru-Phos	TBAB	1,4-Dioxane	Trace
23	$K_2S_2O_5$	DPE-Phos	TBAB	1,4-Dioxane	28
24	$K_2S_2O_5$	IPr·HCl	TBAB	1,4-Dioxane	Trace
25[c]	$K_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	98
26[c,d]	$K_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	21
27[c,e]	$K_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	TBAB	1,4-Dioxane	Trace
28[f]	$K_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	TBAB/HBF_4	1,4-Dioxane	84
29[g]	$K_2S_2O_5$	$P^tBu_3{\cdot}HBF_4$	TBAB/HBF_4	1,4-Dioxane	97

[a] Reaction conditions: 4-methylbenzene **1a** (0.5 mmol), sulfate (0.5 mmol), morpholin-4-amine **2a** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), additive (1.5 equiv.), solvent (2.0 mL). [b] Isolated yield based on 4-methylbenzene **1a**. [c] In the presence of $P^tBu_3{\cdot}HBF_4$ (20 mol%). [d] The reaction occurred at 60 °C. [e] The reaction was performed at 50 °C. [f] In the presence of HBF_4 (10 mol%). [g] In the presence of HBF_4 (20 mol%).

occurred in the presence of $P^tBu_3{\cdot}HBF_4$ (10 mol%) and HBF_4 (20 mol%) (Table 1, entry 29). A lower reactivity was observed when the catalytic amount of palladium catalyst and phosphine ligand was reduced to 2 mol% (data not shown in Table 1).

The generality of this palladium-catalyzed three-component reaction of aryl iodides, potassium metabisulfite, with hydrazines was then explored under the optimized conditions (5 mol% of $Pd(OAc)_2$, 10 mol% of $P^tBu_3{\cdot}HBF_4$, 20 mol% of HBF_4, 1.5 equiv. of TBAB, 1,4-dioxane, 80 °C). The results are summarized in Table 2. This palladium-catalyzed aminosulfonylation was found to be workable with aryl iodides **1** bearing electron-withdrawing and -donating substituents on the aromatic backbone. Notably, amino and hydroxyl functionalities were all tolerated, and the corresponding aryl *N*-aminosulfonamides **3** were obtained in good yields. For instance, 4-hydroxyphenyl iodide reacted with morpholin-4-amine **2a** leading to the product **3h** in 71% yield. The reaction of 4-aminophenyl iodide with morpholin-4-amine **2a** gave rise to the corresponding product **3i** in 83% yield. Moreover, the ester incorporated phenyl iodide was compatible as well in this reaction, although the final outcome is not as good as expected (**3p**, 55% yield).

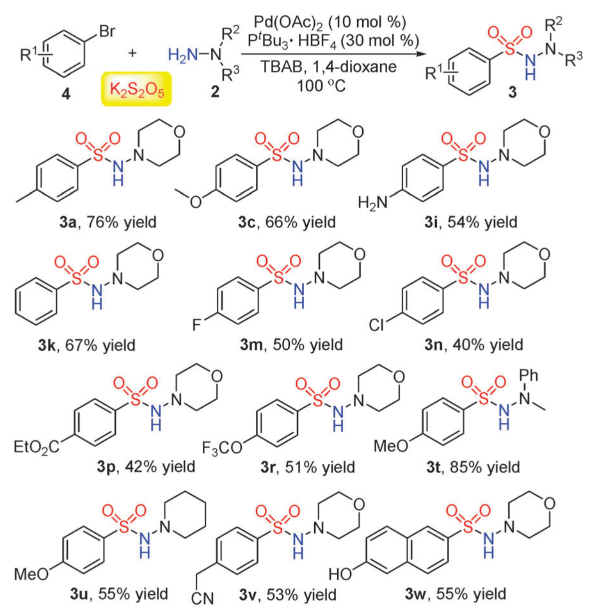
Table 2 Palladium-catalyzed three-component reaction of aryl iodide **1**, potassium metabisulfite, with hydrazines **2**[a]



[a] Isolated yield based on aryl iodide **1**. [b] 10 mol% of $Pd(OAc)_2$, 30 mol% of $P^tBu_3{\cdot}HBF_4$. [c] 5 mol% of $Pd(OAc)_2$, 20 mol% of $P^tBu_3{\cdot}HBF_4$.

Furthermore, the substituents of chloro and bromo on the aromatic ring were retained under the standard conditions. Additionally, other hydrazines **2** such as piperidin-1-amine and 1-methyl-1-phenylhydrazine were examined in the reactions, which provided the expected products in good yields.

Table 3 Palladium-catalyzed three-component reaction of aryl bromide **4**, potassium metabisulfite, with hydrazines **2**[a]



[a] Isolated yield based on aryl bromide **4**.

However, anilines and aliphatic amines are not workable under the optimal conditions, and the results are similar to the previous reports.[6,7]

In a second set of experiments, the scope of the process with respect to aryl bromides was explored. The results are presented in Table 3. Interestingly, we found that the reactions proceeded smoothly in the presence of 30 mol% of $P^tBu_3\cdot HBF_4$ at 100 °C. Again, amino, hydroxyl and ester groups were all compatible during the reaction process. Cyano and chloro groups survived during the transformation. From the results, potassium metabisulfite as the source of sulfur dioxide worked well under the palladium-catalyzed aminosulfonylation of aryl halides.

In summary, we have demonstrated that potassium metabisulfite is an excellent equivalent of sulfur dioxide in the reaction of palladium-catalyzed aminosulfonylation. Aryl *N*-aminosulfonamides could be easily produced *via* a palladium-catalyzed three-component reaction of aryl halides, potassium metabisulfite, with hydrazines. Not only aryl iodides but also aryl bromides are workable during the reaction process. Employing inorganic sulfites as the source of sulfur dioxide in other transition metal-catalyzed reactions is under investigation currently, and the results will be reported in due course.

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Notes and references

1 (*a*) S. D. Burke, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, Chichester, 1995, vol. 7, p. 4688; (*b*) Z. Florjańczyk and D. Raducha, *Pol. J. Chem.*, 1995, **69**, 481; (*c*) P. Vogel, M. Turks, L. Bouchez, D. Markovic, A. Varela-Álvarez and J. A. Sordo, *Acc. Chem. Res.*, 2007, **40**, 931; (*d*) *Ullmann's Encyclopedia of Industrial Chemistry*, ed. B. Elvers, S. Hawkins and W. Russey, VCH, Weinheim, Germany, 5th edn, 1994, vol. A25.

2 (*a*) P. Vogel and J. A. Sordo, *Curr. Org. Chem.*, 2006, **10**, 2007; (*b*) R. V. Hoffmann, *Org. Synth.*, 1981, **60**, 121; (*c*) C. P. Tsonis, in *Polymeric Materials Encyclopedia*, ed. J.C. Salamone, CRC Press, New York, 1996, vol. 9, p. 6866; (*d*) G. J. Kubas, *Acc. Chem. Res.*, 1994, **27**, 183; (*e*) W. A. Schenk, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 98; (*f*) G. J. Kubas, *Inorg. Chem.*, 1979, **18**, 182; (*g*) D. M. P. Mingos, *Transition Met. Chem.*, 1978, **3**, 1; (*h*) A. Wojcicki, *Adv. Organomet. Chem.*, 1974, **12**, 31; (*i*) W. Kitching and C. W. Fong, *Organomet. Chem. Rev., Sect. A*, 1970, **5**, 281; (*j*) A. Wojcicki, *Acc. Chem. Res.*, 1971, **4**, 344.

3 (*a*) G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, *J. Am. Chem. Soc.*, 1956, **78**, 4743; (*b*) M. M. Rogic and D. Masilamani, *J. Am. Chem. Soc.*, 1977, **99**, 5219; (*c*) T. Hamada and O. Yonemitsu, *Synthesis*, 1986, 852; (*d*) J.-P. Wu, J. Emeigh and X.-P. Su, *Org. Lett.*, 2005, **7**, 1223; (*e*) L. C. Bouchez, S. R. Dubbaka, M. Turks and P. Vogel, *J. Org. Chem.*, 2004, **69**, 6413; (*f*) L. C. Bouchez, M. Turks, S. Reddy Dubbaka, F. Fonquerne, C. Craita, S. Laclef and P. Vogel, *Tetrahedron*, 2005, **61**, 11473; (*g*) V. Narkevitch, K. Schenk and P. Vogel, *Angew. Chem., Int. Ed.*, 2000, **39**, 1806.

4 (*a*) H. S. Klein, *Chem. Commun.*, 1968, 377; (*b*) W. Keim and J. Herwig, *J. Chem. Soc., Chem. Commun.*, 1993, 1592; (*c*) J. Herwig and W. Keim, *Inorg. Chim. Acta*, 1994, **222**, 381; (*d*) W. Keim, J. Herwig and G. Pelzer, *J. Org. Chem.*, 1997, **62**, 422; (*e*) G. Pelzer and W. Keim, *J. Mol. Catal. A: Chem.*, 1999, **139**, 235; (*f*) L. M. Wojcinski, M. T. Boyer and A. Sen, *Inorg. Chim. Acta*, 1998, **270**, 8; (*g*) U. M. Dzhemilev and R. V. Kunakova, *J. Organomet. Chem.*, 1993, **455**, 1; (*h*) G. Pelzer, J. Herwig, W. Keim and R. Goddard, *Russ. Chem. Bull.*, 1998, **47**, 904.

5 W. J. Mahn, in *Academic Laboratory Chemical Hazards Guidebook*, ed.Van Norstrand Reinhold, New York, 1991, p. 264.

6 (*a*) B. Nguyen, E. J. Emmett and M. C. Willis, *J. Am. Chem. Soc.*, 2010, **132**, 16372; (*b*) H. Woolven, C. González-Rodríguez, I. Marco, A. L. Thompson and M. C. Willis, *Org. Lett.*, 2011, **13**, 4876; (*c*) E. J. Emmett, C. S. Richards-Taylor, B. Nguyen, A. Garcia-Rubia, B. R. Hayter and M. C. Willis, *Org. Biomol. Chem.*, 2012, **10**, 4007.

7 S. Ye and J. Wu, *Chem. Commun.*, 2012, **48**, 7753.