Organic LETTERS
Letter
pubs.acs.org/OrgLett

The Reaction of Grignard Reagents with Bunte Salts: A Thiol-Free Synthesis of Sulfides

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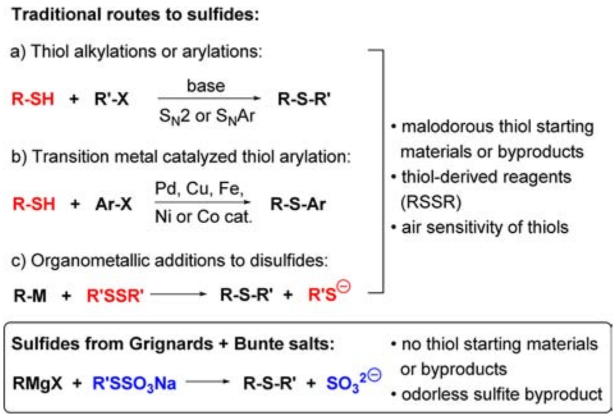
Supporting Information

ABSTRACT: S-Alkyl, S-aryl, and S-vinyl thiosulfate sodium salts (Bunte salts) react with Grignard reagents to give sulfides in good yields. The S-alkyl Bunte salts are prepared from odorless sodium thiosulfate by an S_N2 reaction with alkyl halides. A Cu-catalyzed coupling of sodium thiosulfate with aryl and vinyl halides was developed to access S-aryl and S-vinyl Bunte salts. The reaction is amenable to a broad structural array of Bunte salts and Grignard reagents. Importantly, this route to sulfides avoids the use of malodorous thiol starting materials or byproducts.

In 1874, Hans Bunte reported the reaction of ethyl bromide with sodium thiosulfate to yield S-ethyl thiosulfate sodium salt as a crystalline solid.[1] While Bunte's aim in this work was clarification of the structure of sodium thiosulfate, the S-alkyl thiosulfate salts which bear his name have subsequently proven to be valuable synthetic intermediates.[2] Acidic hydrolysis of Bunte salts yields the corresponding thiols,[1,3] while addition of nucleophiles such as thiols,[4] Na_2S,[5] or cyanide[6] yields disulfides, trisulfides, and thiocyanates, respectively. Bunte salts are conveniently prepared by the reaction of odorless and inexpensive sodium thiosulfate with alkyl halides (Scheme 1).[7] Bunte salts are easy to handle crystalline solids, even with highly lipophilic organic moieties, and generally have little to no odor.

Scheme 1. Preparation and Properties of Bunte Salts

Scheme 2. Methods for Sulfide Synthesis



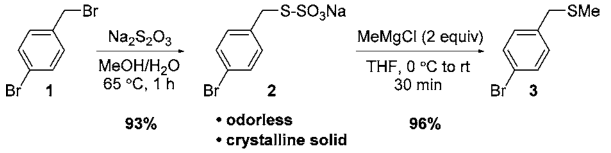
Sulfides are present in many natural products and pharmaceuticals.[8] In addition, sulfides are often precursors to higher oxidation state moieties such as sulfoxides, sulfones, and sulfoximines. The synthesis of sulfides is often performed by thiol alkylation or arylation, with or without the use of a transition metal catalyst (Scheme 2, methods a and b),[9,10] or by the addition of an organometallic reagent to a disulfide (method c).[11] These methods have the drawback of either using malodorous thiols as starting materials (methods a and b) or generating thiols as stoichiometric byproducts (method c).[12] Thiols are notorious for their powerful stench. Indeed, thiols are the major components of skunk spray.[13] The human olfactory system is extremely sensitive to thiols. For example, *tert*-butyl thiol, the odorant added to natural gas to enable detection of leaks, can be smelled at levels of <1 part per billion.[14] Thiols are also air sensitive and are readily oxidized to disulfides by atmospheric oxygen. Because of their potent stench, the use of thiol starting materials or the generation of thiol byproducts, particularly on a large scale, is highly undesirable. It was reasoned that the addition of Grignard reagents to Bunte salts could provide a general route to sulfides without the requirement of thiol starting materials (Scheme 2).[15] In this case, the leaving group would be the water-soluble and odorless sulfite anion rather than a thiolate. This process would also take advantage of the ready availability, either commercially or by *in situ* preparation from the corresponding halides, of a vast array of Grignard reagents. Herein we describe the addition of Grignard reagents to Bunte salts as a mild and general thiol-free route to sulfides.

For exploration of reaction feasibility, Bunte salt **2** was prepared by the reaction of 4-bromobenzyl bromide **1** with sodium

Received: January 8, 2014
Published: February 10, 2014

dx.doi.org/10.1021/ol500067f | *Org. Lett.* 2014, 16, 1196−1199

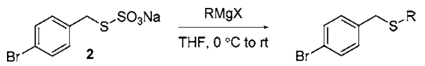
Scheme 3. Synthesis of Bunte Salt 2 and Sulfide 3

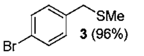
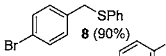
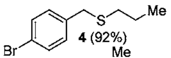
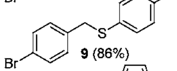
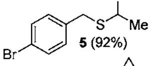
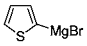
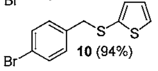
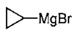
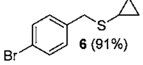
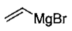
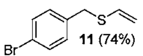
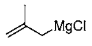
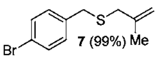
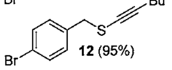


thiosulfate in aqueous methanol (Scheme 3). Salt **2**, like every Bunte salt prepared in this manuscript, was a crystalline solid.[16] Treatment of a slurry of **2** in THF at 0 °C with MeMgCl (2 equiv) and subsequent warming to rt resulted in the formation of sulfide **3** in 96% isolated yield. Importantly, this route to **3** avoids the use of highly malodorous MeSH, NaSMe, 4-bromobenzylthiol, or its salts, or the corresponding disulfides, and instead proceeds through odorless reagents, intermediates, and byproducts.

The scope of the reaction of salt **2** with different Grignard reagents was examined next (Table 1). The reaction with a diverse array of Grignard reagents was possible, giving access to the corresponding sulfides in excellent yields. In addition to alkyl Grignard reagents, methallyl, aryl, heteroaryl, vinyl, and alkynyl Grignard reagents were also effective.

Table 1. Scope of Grignard Reagents[a]

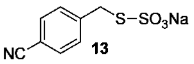
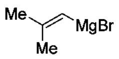
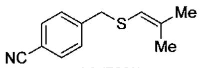
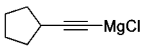
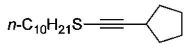
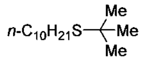
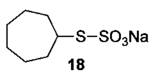
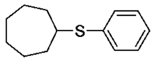
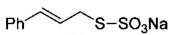
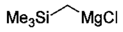
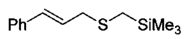
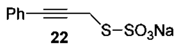
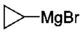
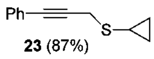
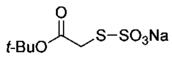
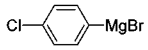
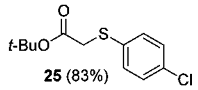
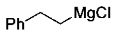
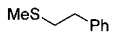


RMgX	product (yield)[b]	RMgX	product (yield)[b]
MeMgCl	 **3** (96%)	PhMgBr	 **8** (90%)
n-PrMgCl	 **4** (92%)	4-$MeOC_6H_4MgBr$	 **9** (86%)
i-PrMgCl	 **5** (92%)		 **10** (94%)
	 **6** (91%)		 **11** (74%)
	 **7** (99%)	Bu—≡—MgCl	 **12** (95%)

[a]Typical reaction conditions: 1 equiv of Bunte salt **2**, 2−3 equiv of Grignard reagent, THF, 0 °C−rt. [b]Isolated yield.

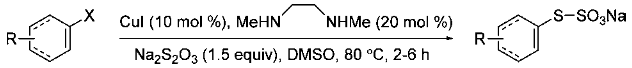
The reaction scope with different alkyl Bunte salts was next explored. The requisite S-alkyl salts were prepared using the same S_N2 reaction conditions employed for the synthesis of **2** in Scheme 3. The reaction of a diverse set of alkyl Bunte salts, including benzyl (entry 1), primary and secondary alkyl (entries 2−4), allyl (entry 5), propargyl (entry 6), *tert*-butoxycarbonylmethyl (entry 7) and methyl (entry 8), was possible with a broad array of Grignard reagents (Table 2). The use of *tert*-BuMgCl enabled the synthesis of an alkyl *tert*-butyl sulfide (entry 3) without the use or generation of extremely malodorous *tert*-butyl thiol.[14] Functional groups such as a nitrile (entry 1), trimethylsilyl (entry 5), *tert*-butyl ester (entry 7), and aryl chloride (entry 7) were tolerated.

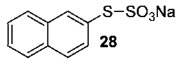
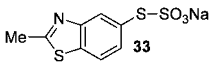
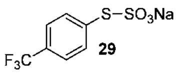
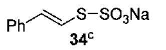
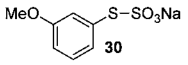
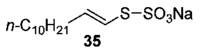
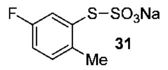
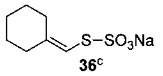
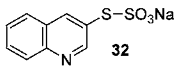
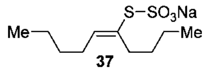
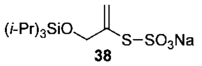
Table 2. Scope of Alkyl Bunte Salts[a]

entry	Bunte salt	RMgX	product (yield)[b]
1	 **13**		 **14** (78%)
2	n-$C_{10}H_{21}S\text{–}SO_3Na$ **15**		 **16** (91%)
3	**15**	t-BuMgCl	 **17** (82%)
4	 **18**	PhMgBr	 **19** (97%)
5	 **20**		 **21** (84%)
6	 **22**		 **23** (87%)
7	 **24**		 **25** (83%)
8	$MeS\text{–}SO_3Na$ **26**		 **27** (89%)

[a]Typical reaction conditions: 1 equiv of Bunte salt, 2−3 equiv of Grignard reagent, THF, 0 °C−rt. [b]Isolated yield.

Table 3. Cu-Catalyzed Aryl or Vinyl Bunte Salt Synthesis[a]



product	yield[b]	product	yield[b]
 **28**	82%	 **33**	73%
 **29**	85%	 **34**[c]	76%
 **30**	73%	 **35**	89%
 **31**	86%	 **36**[c]	88%
 **32**	75%	 **37**	72%
		 **38**	66%

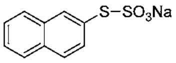
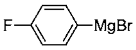
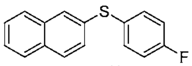
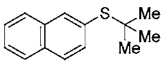
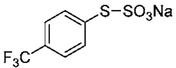
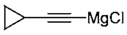
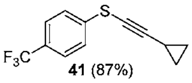
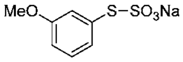
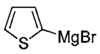
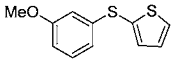
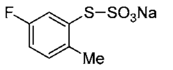
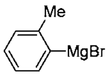
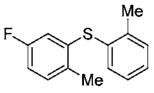
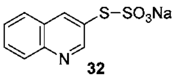
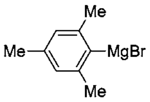
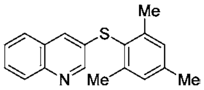
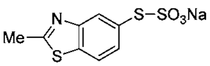
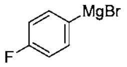
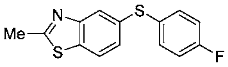
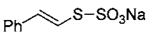
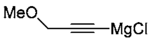
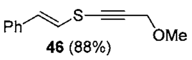
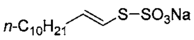
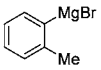
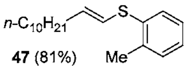
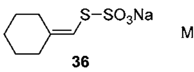
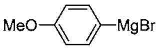
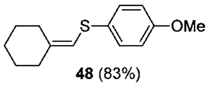
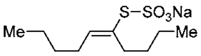
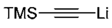
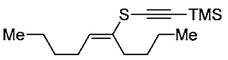
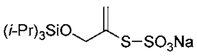
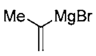
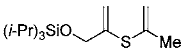
[a]Typical reaction conditions: 1 equiv of aryl or vinyl halide, 1.5 equiv of $Na_2S_2O_3$, 0.1 equiv of CuI, 0.2 equiv of DMEDA, DMSO, 80 °C, 2−6 h. [b]Isolated yield. [c]Starting material was the corresponding vinyl bromide.

S-Aryl Bunte salts would provide access to a more complete range of sulfides, including diaryl sulfides, which represent a common target of transition metal catalyzed thiol arylation and a prevalent moiety in pharmaceuticals.[8,10] Aryl Bunte salts have traditionally been prepared by sulfonylation of aryl thiols[17] or by the reaction of sodium sulfite with aryl disulfides or aryl sulfenyl chlorides.[18] Janeba and co-workers recently described the conversion of aryl thiocyanates to aryl Bunte salts with sodium sulfite.[19] The above procedures require the use of aryl thiol or aryl thiol-derived starting materials, the use of less readily available starting materials (aryl thiocyanates), or the production of toxic sodium cyanide as a byproduct. A metal-catalyzed coupling of aryl halides with sodium thiosulfate would represent a more general route to aryl Bunte salts and would employ widely available aryl halide starting materials. Fu and Guo reported a Pd-catalyzed coupling of sodium thiosulfate with aryl halides in which the putative Bunte salts were not isolated but reduced *in situ* with Zn/HCl to aryl thiols.[20] While these conditions were effective for aryl thiol synthesis, our attempts to isolate the intermediate Bunte salts resulted in low yields mainly due to significant thiol and disulfide formation. After subsequent screening, we discovered a mild Cu-catalyzed coupling which gave aryl Bunte salts cleanly without thiol or disulfide byproducts. The use of CuI (10 mol %) as the catalyst, Buchwald's *N,N′*-dimethylethylene diamine (DMEDA, 20 mol %)[21] as the ligand, and DMSO as the solvent at 80 °C cleanly coupled aryl iodides with sodium thiosulfate (Table 3).[22] The products were conveniently isolated by direct crystallization on addition of aqueous NaCl solution.[23] The reaction was amenable to aryl iodides bearing ortho, meta, and para substitution, as well as to heterocyclic iodides. In addition, vinyl bromides and iodides were found to be equally competent substrates and gave access to vinyl Bunte salts in excellent yields. The geometric integrity of the starting vinyl halide was maintained during the cross-coupling (salts **34**, **35**, and **37**). It is noteworthy that vinyl Bunte salts are not readily accessible by any alternative methods.

With a variety of aryl and vinyl Bunte salts in hand, we next explored their reaction with Grignard reagents (Table 4). Aryl Bunte salts reacted smoothly with Grignard reagents to give a variety of sulfides in good yields (entries 1−7). The use of aryl and heteroaryl Grignards provided a convenient thiol-free route to diaryl sulfides. Relatively sterically hindered diaryl sulfides were readily prepared (entries 5 and 6). The reaction of vinyl Bunte salts gave access to vinyl sulfides (entries 8−12). Notably, this methodology gives a direct route to vinyl alkynyl (entries 8 and 11) and divinyl (entry 12) sulfides which are not readily accessible by other methods.[24,25] The use of an alkynyl lithium was also effective (entry 11).

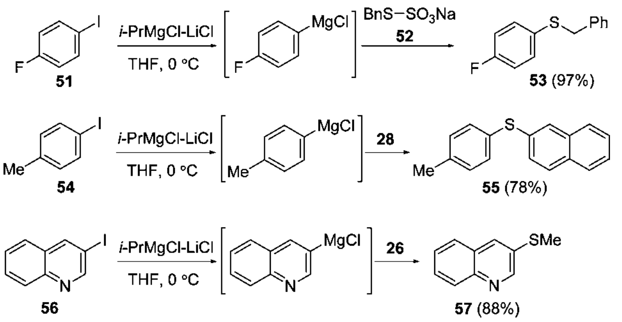
Knochel's protocol for halogen/magnesium exchange with *i*-PrMgCl-LiCl has been shown to be a powerful and convenient method for *in situ* aryl Grignard generation.[26] The formation of aryl Grignard reagents from the corresponding aryl iodides using Knochel's method followed by Bunte salt addition was also effective for sulfide formation (Scheme 4).

Table 4. Scope of Aryl and Vinyl Bunte Salts[a]

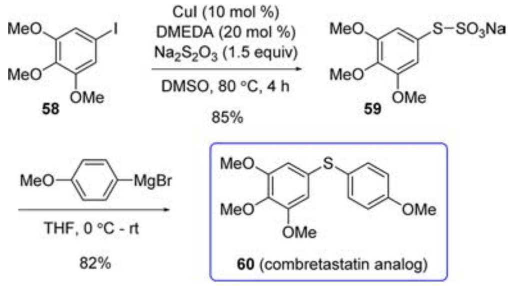
entry	Bunte salt	RMgX	product (yield)[b]
1	 **28**		 **39** (92%)
2	**28**	*t*-BuMgCl	 **40** (68%)
3	 **29**		 **41** (87%)
4	 **30**		 **42** (73%)
5	 **31**		 **43** (82%)
6	 **32**		 **44** (85%)
7	 **33**		 **45** (76%)
8	 **34**		 **46** (88%)
9	 **35**		 **47** (81%)
10	 **36**		 **48** (83%)
11	 **37**		 **49** (74%)
12	 **38**		 **50** (76%)

[a]Typical reaction conditions: 1 equiv of Bunte salt, 2−3 equiv of Grignard reagent, THF, 0 °C−rt. [b]Isolated yield.

Scheme 4. Reactions Using *in Situ* Generated Grignard



Scheme 5. Thiol-Free Combretastatin Analog Synthesis



The sulfide formation was applied to a synthesis of the potent combretastatin analog **60** (Scheme 5).[27] Bunte salt **59** was prepared from iodide **58** in 85% yield by Cu-catalyzed coupling with sodium thiosulfate. Reaction of **59** with 4-methoxyphenylmagnesium bromide furnished sulfide **60** in 82% yield. While previous syntheses of **60** used highly malodorous arylthiol intermediates, the present synthesis proceeds with odorless intermediates and reagents.

In summary, the reaction of Grignard reagents with Bunte salts has been described. The procedure provides access to sulfides without the use of malodorous and air sensitive thiol starting materials, byproducts, or thiol-derived reagents. The Bunte salts are readily prepared from alkyl or aryl halides and odorless and inexpensive sodium thiosulfate. A Cu-catalyzed coupling reaction was developed for the synthesis of aryl and vinyl Bunte salts and provides the first general and direct route to these valuable compounds. The resultant accessibility of aryl and vinyl Bunte salts should facilitate further explorations of their utility in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data (^{1}H and ^{13}C NMR). 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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