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An Efficient Protecting-Group-Free Synthesis of Vinylic Sulfoximines via Horner–Wadsworth–Emmons Reaction

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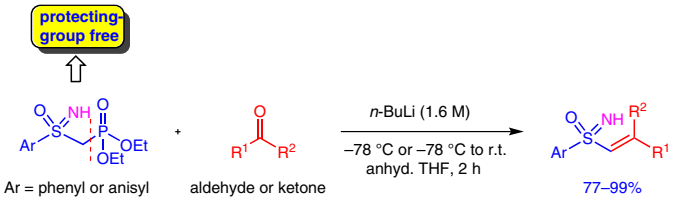

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Abstract Herein, we report a convenient synthesis of aryl-substituted (*E*)-vinylic *NH*-sulfoximines via the Horner–Wadsworth–Emmons reaction without the use of protection–deprotection group strategies.

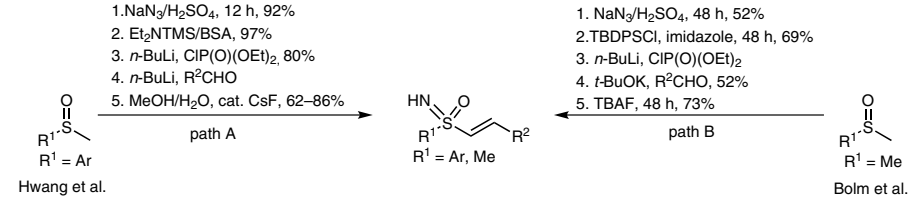
Key words phosphonate, Horner–Wadsworth–Emmons, vinylic sulfoximine

Sulfoximines are chiral analogues (isosteres) of sulfones, in which one of the sulfone oxygen atoms has been replaced by a nitrogen atom (=NR); the new imine nitrogen substituent offers interesting opportunities for adjusting the properties of the parent molecule. Not surprising, such compounds are gaining increased interest for the design of new drugs[1] and pesticidal agents.[2] Sulfoximines are of importance also in the area of new antibiotics.[3]

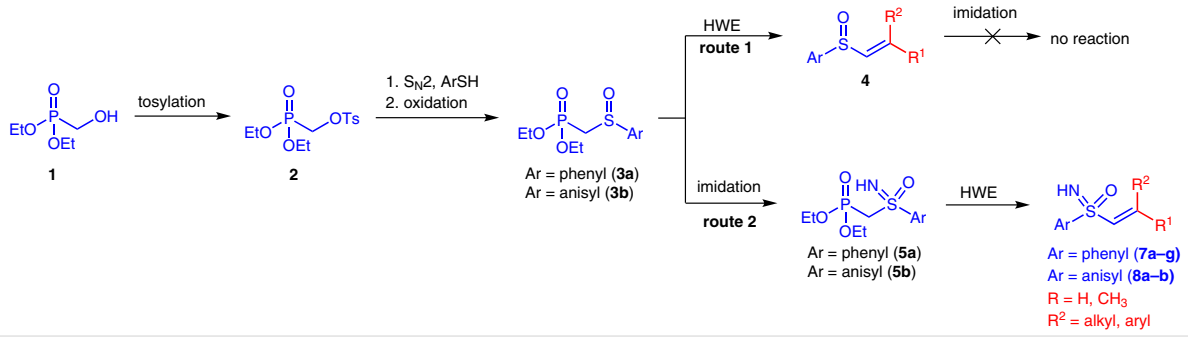
In addition, vinylic sulfoximines have been a widely used functional group in organic chemistry; for example, in asymmetric synthesis[4] as a chiral auxiliaries,[5] ligands,[6] Michael acceptors,[7] and as dienophiles in pericyclic reactions.[8] Vinylic sulfoximines have also been used as precursors in the synthesis of allylic sulfoximines.[9] Apart from that, derivatives with medicinal value such as calcemic inhibitory activity have also been reported.[10]

A number of methods is available in the literature for the preparation of vinylic sulfoximines. In most cases these molecules are accessed via Horner–Wadsworth–Emmons (HWE)[10,11] (Scheme 1) or Peterson olefination[12] reactions, in which the imine nitrogen is subject to a protection–deprotection strategy. Apart from these two protocols, vinylic sulfoximines have been prepared by hydroxyalkylation–elimination of metalated alkyl sulfoximines[13] and carbometalation of alkynyl sulfoximines.[14]

However, these methods suffer from limited substrate scope and multistep synthesis with overall moderate to low yields; furthermore, the products are N-protected/substituted vinylic sulfoximines, in which removal of the protecting groups in some cases is challenging. To the best of our knowledge, there are no literature reports on a straightforward synthesis to vinylic *NH*-sulfoximines that do not require a protection–deprotection strategy. Herein, we present a new and facile method that not only bridges this synthetic gap but also provided N-deprotected sulfoximines in very good to excellent yields.



Scheme 1 General synthetic routes to vinylic *NH*-sulfoximines have relied on a protection–deprotection strategy



Scheme 2 Two routes to access vinylic *NH*-sulfoximines

Our procedure is based on the use of substituted or unsubstituted diethyl(phenylsulfinylmethyl)phosphonate **3a** or **3b** as the starting material. Phosphonates **3a** or **3b** are readily available from commercial diethyl phosphonomethanol (**1**) that, after tosylation, gave (diethoxyphosphoryl)methyl-4-methylbenzenesulfonate (**2**) followed by nucleophilic substitution with aryl thiol to provide the respective thiophosphonate that was oxidized with Oxone at 0 °C to furnish the required products **3a** and **3b** (Scheme 2).

With compound **3a** in hand, we attempted to prepare vinyl sulfoximine from diethyl(phenylsulfinylmethyl)phosphonate **3** and benzaldehyde under HWE reaction conditions (*n*-BuLi, –78 °C to r.t.) followed by imidation using *o*-(mesitylenesulfonyl)hydroxylamine (MSH, route 1).[15] However, this strategy failed due to complications most likely resulting from the vinylic bond in compound **4**.[16] Instead, we performed the imidation of compound **3a** using MSH to yield diethyl(phenylsulfonimidoylmethyl)phosphonate (**5a**) as the first reaction step (route 2). The subsequent reaction with benzaldehyde (**6a**) under HWE reaction conditions (*n*-BuLi, –78 °C to r.t.) successfully provided the vinylic sulfoximine **7a**, albeit in low yield (19%).

The reaction of compound **5a** with benzaldehyde (**6a**) was chosen as the model reaction for optimization. Firstly, in order to check the influence of different bases on reaction yield, we attempted the reaction with the different bases (*t*-BuOK, *t*-BuONa, LiHMDS) in THF at –78 °C to r.t. Unfortunately, there was no improvement in yield compared to *n*-BuLi at –78 °C to r.t.

As temperature plays a crucial role in the *n*-BuLi promoted reaction, we concentrated on optimizing the reaction temperature, and the reaction was examined at –78 to 0 °C. Gratifyingly, performing the reaction at –78 °C afforded vinyl sulfoximine **7a** in 98% yield and with complete *E* selectivity (Table 1, entry 1).

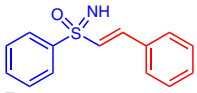
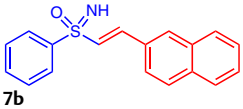
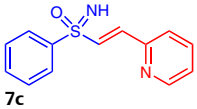
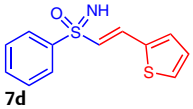
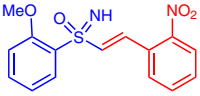
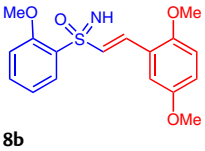
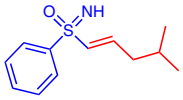
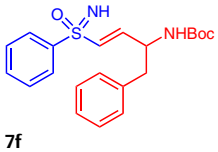
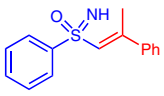
With these optimal conditions, the substrate scope was expanded to a wide range of aldehydes such as aliphatic, aromatic, and heterocyclic aldehydes, and the reaction was found to proceed smoothly at –78 °C as represented in Table 1. The reaction could be extended to simple polycyclic aromatic compounds such as **6b** that also worked well and gave **7b** in 99% yield (Table 1, entry 2). Furthermore, the heterocyclic aldehydes **6c** and **6d** proceeded smoothly and gave the products **7c** and **7d** in 93% and 96% yield, respectively, with complete *E* selectivity (Table 1, entries 3 and 4). In addition, other aromatic aldehydes with electron-donating and electron-withdrawing groups such as **6e** and **6f**, when reacted with **5b**, provided the corresponding products **8a** and **8b** in 96% and 95% yield (Table 1, entries 5 and 6). Aliphatic aldehyde **6g** also worked well for this reaction and offered the respective product **7e** in 98% yield (Table 1, entry 7). In an attempt to utilize a highly functionalized substrate, we reacted *N*-Boc-protected amino aldehyde **6h** to obtain the desired product **7f** in 91% yield.[17] Reaction with ketone substrate **6i** did not proceed at –78 °C, so the reaction temperature was increased to room temperature after addition of the ketone at –78 °C; this gave the desired product **7g** in a moderate yield of 77% (Table 1, entry 9)[18] but with the poor *E*/*Z* selectivity typically seen for ketones under HWE conditions.

One plausible explanation for why protection of the imine nitrogen is not needed and NH deprotonation is not observed with *n*-BuLi under these reaction conditions can be found in a theoretical paper by Bharatam et al. Based on high level quantum mechanical calculations they proposed that the S–N bond in sulfoximines is best described as a single-bond ionic interaction.[19] Thus, we anticipate that *n*-BuLi at –78 °C first abstracts a proton from the active methylene group of **5a** or **5b** (Scheme 3) rather than from the imine (NH) due to the presence of an already fully developed negative charge at the nitrogen atom.

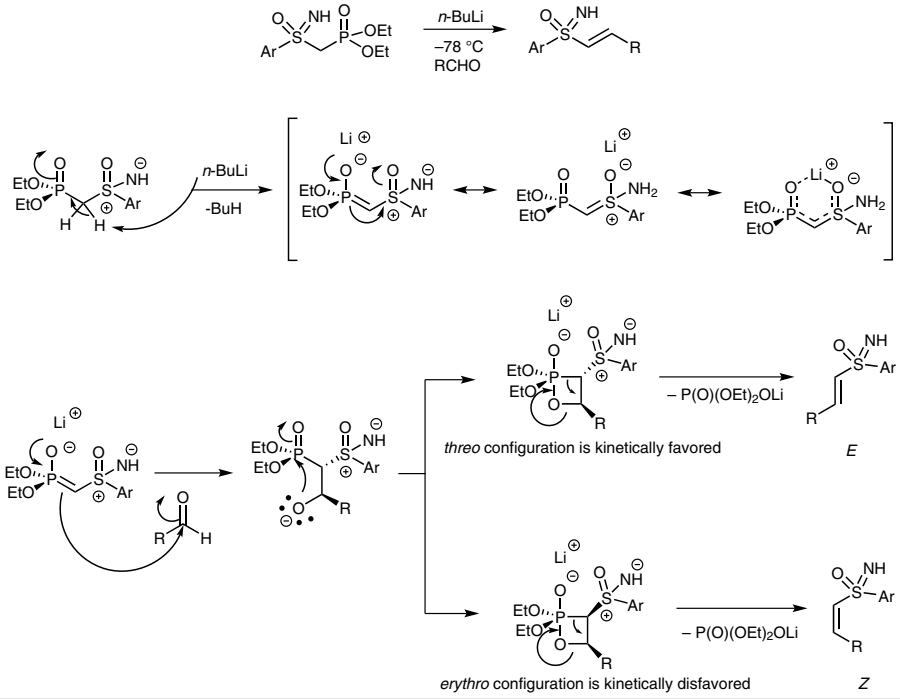
The active methylene carbanion is stabilized by resonance with the diethyl phosphonate and sulfoximine groups as shown in Scheme 3. The most stable and reactive intermediate reacts with the carbonyl compound, and the reaction proceeds through a kinetically favored *threo* configuration to avoid steric repulsions in the oxaphosphetane transition state, leading to the (*E*)-vinylic sulfoximine as the major product as confirmed analysis of ^{1}H NMR coupling constants (*J*). The plausible reaction mechanism is depicted in Scheme 3.

Table 1 Reaction of Compounds **5a**,**b** with Various Aldehydes for the Synthesis of Vinylic *NH*-Sulfoximines[a]

5 **6** **7**

Entry	5	Aldehyde/ketone	Temp (C)[c]	Product **7**	Yield (%)[b]	*E*/*Z*
1	**5a**	**6a** R^1 = H, R^2 = Ph	–78	 **7a**	98	100:0
2	**5a**	**6b** R^1 = H, R^2 = $C_{10}H_7$	–78	 **7b**	99	100:0
3	**5a**	**6c** R^1 = H, R^2 = C_5H_4N	–78	 **7c**	93	100:0
4	**5a**	**6d** R^1 = H, R^2 = C_4H_3S	–78	 **7d**	96	100:0
5	**5b**	**6e** R^1 = H, R^2 = $C_6H_4NO_2$	–78	 **8a**	96	100:0
6	**5b**	**6f** R^1 = H, R^2 = $C_8H_9O_2$	–78	 **8b**	95	100:0
7	**5a**	**6g** R^1 = H, R^2 = *i*-Bu	–78	 **7e**	98	100:0
8	**5a**	**6h** R^1 = H, R^2 = $C_{13}H_{18}NO_2$	–78	 **7f**	91	100:0
9	**5a**	**6i** R^1 = Me, R^2 = Ph	–78 to r.t.	 **7g**	77	64:56

[a] Substrate **5a** or **5b** (1 equiv), aldehyde or ketone (1.2 equiv), *n*-BuLi (1.2 equiv). Reaction quenched with sat. NH_4Cl.
[b] Isolated yields.



Scheme 3 Plausible reaction mechanism

In conclusion, we have developed a novel methodology to access vinylic *NH*-sulfoximines, removing the use of protection and deprotection group strategies. The procedure is compatible with a wide range of substrates and functional groups and offers excellent yields and *E*-selectivity. We anticipate that the current methodology will find broad utility for the synthesis of vinylic sulfoximines as a precursor in organic synthesis and medicinal chemistry applications.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561573.

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(17) **General Procedure for the Synthesis of Compounds 7a–f and 8a,b**

n-BuLi (1.2 equiv of 1.6 M solution in hexane) was added to a solution of diethylphenylsulfonimidoylmethylphosphonate (1.0 equiv) in dry THF (4 mL) kept at –78 °C. The reaction was stirred for 1 h before sequential addition of aldehyde (1.3 equiv). Then the resulting reaction mixture was stirred at –78 °C for 1 h. After completion, the reaction mixture was neutralized with NH_4Cl and extracted with EtOAc (3 × 20 mL) to give the title product.

(*E*)-[2-(Phenylsulfonimidoyl)vinyl]benzene (7a)

^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (2 H, m, Ar*H*), 7.63 (1 H, d, *J* = 15.2 Hz), 7.58–7.48 (3 H, m, Ar*H*), 7.46–7.44 (2 H, m, Ar*H*), 7.36–7.33 (3 H, m, Ar*H*), 6.96 [1 H, d, *J* = 15.2 Hz, (*E*)-*CH*=CH]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 141.7, 132.8, 132.6, 130.9, 130.0, 129.4, 129.3, 129.0, 128.5, 128.3 (2), 127.9 (2). IR (ATR): ν = 3262, 3059, 1703, 1614, 1575, 1215, 1070, 744, 709, 607 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}NOSH^+$: 244.0791; found: 244.0811 [M + H]$^+$.

(18) **General Procedure for the Synthesis of Compound 7g**

n-BuLi (1.2 equiv of 1.6 M solution in hexane) was added to a solution of diethylphenylsulfonimidoylmethylphosphonate (1.0 equiv) in dry THF (4 mL) kept at –78 °C. The reaction was stirred for 1 h before sequential addition of acetophenone (1.3 equiv). Then the resulting reaction mixture was stirred at r.t. for 1 h. The reaction mixture was then neutralized with aq NH_4Cl and extracted with EtOAc (3 × 20 mL) to give the title product after workup.

(*E*)-(2-Phenylprop-1-enylsulfonimidoyl)benzene (7g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06–8.04 (2 H, m, Ar*H*), 7.63–7.53 (4 H, m, Ar*H*), 7.44–7.42 (2 H, m, Ar*H*), 7.38–7.33 (2 H, m, Ar*H*), 6.89 (1 H, s, *CH*=C), 2.44 (3H , d, *J* = 1 Hz, CH=CCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9, 133.4, 130.2, 129.5 (3 C), 128.9 (3 C), 128.0 (3 C), 126.5 (2 C), 16.9. IR (ATR): ν = 2958, 2920, 2849, 2171, 2018, 1456, 1123, 1049, 623, 499 cm^{-1}. HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for for $C_{15}H_{15}NOSH^+$: 258.0947; found: 258.0967 [M + H]$^+$.

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