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Wittig–Horner mediated synthesis of 4-vinyl sulfide derivatives of pyrazoles

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ABSTRACT

The synthesis of a series of 4-vinyl sulfide derivatives of 1,3-diarylpyrazoles, including their corresponding sulfoxides and sulfones, is reported. Access to the target vinyl sulfides was stereoselectively achieved, in moderate to good yields, by the *n*-BuLi-mediated Wittig–Horner reaction of 4-formylpyrazoles with arylthiophosphonates and α-chloroarylthiophosphonates in dimethoxyethane. Their oxidation with H_2O_2 in AcOH and *m*CPBA in CH_2Cl_2 afforded satisfactory yields of the expected vinyl sulfoxides and vinyl sulfones, respectively. Enrichment in the more stable isomers during both oxidation processes was detected and a plausible general mechanistic explanation was given to these observations.

Pyrazole is the key structural motif of a handful of natural products and many synthetic compounds. Pyrazole derivatives exhibit a range of valuable biological activities;[1] furthermore, some good selling pharmaceuticals are also pyrazole-based drugs, like the anti HIV atorivodine[2a] and the NSAIDs drugs etoricoxib, celecoxib,[2b] and deracoxib.[2c]

On the other hand, organochalcogen compounds play an important role in modern organic synthesis;[3] some of them also display very useful biological activities.[4] The vinyl chalcogenides are a distinguished group of organochalcogens that has attracted considerable attention in recent years.[5] Among them, vinyl sulfides are particularly interesting, serving as intermediaries for various organic transformations.[6] They are usually prepared by addition of thiols or thiolates to alkynes[7] and by reaction of thiols with vinyl halides,[8] under metal-catalysis. However, the most useful strategies toward these compounds relay on Wittig and Wittig–Horner reactions.[9]

Despite the abundant literature on polysubstituted pyrazolic compounds, only scattered syntheses of their 4-vinylsulfide derivatives have been reported,[10] and none of them of a trisubstituted α-halo derivative. Many congeners have been obtained by means of a Knoevenagel condensation; however, only a single case reports their access through a Wittig-type reaction, where the carbonyl partner is part of a pyrazole unit.[11]

Therefore, in pursuit of our continued interest in the preparation of new vinyl chalcogenides based on the Wittig and Wittig–Horner reactions,[12] herein we report our study of the synthesis of vinyl sulfides (**1**), sulfoxides (**2**) and sulfones (**3**) derived from 4-formylpyrazoles (**4**) by their Wittig–Horner reaction with **5** and **6** (Scheme 1).

The starting 4-formylpyrazoles **4a–c** were prepared in 49–65% overall yield by reaction of the easily available ketones **7a–c** with phenylhydrazine under AcOH catalysis (Scheme 2), followed by cyclization and subsequent formylation of the resulting hydrazones **8a–c**[13] with the Vilsmeier–Haack reagent ($POCl_3$/DMF).[14]

The thiophosphonates **5a,b** were prepared in 53–55% yield from diethyl phosphite and paraformaldehyde, followed by tosylation[15a] of the so formed hydroxymethyl phosphonate, and tosylate displacement with the appropriate arenethiol (Scheme 3).[15b] Finally, the corresponding α-chlorothiophosphonates **6a,b** were obtained (87% yield) by chlorination of **5a,b** with NCS.[15c]

In order to optimize the proposed Wittig–Horner olefination toward the expected vinyl sulfide **1a**, the model reaction between the phosphonic ester derivative **5a** and the pyrazole aldehyde **4a** was examined.[16] Initial studies were carried out in THF, changing the reaction temperature and time, and employing a series of bases such as NaH, NaOMe, *t*-BuOK, and *n*-BuLi. Some other solvents and phase transfer catalysts (PTC) were also tested.

As shown in Table 1, low yields and stereoselectivities (determined by ^{1}H NMR) were obtained with NaH and NaOMe in THF (entries 1 and 2), and no product was observed when *t*-BuOK

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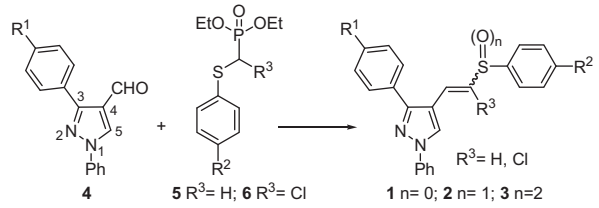
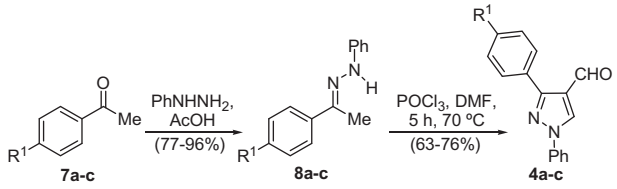
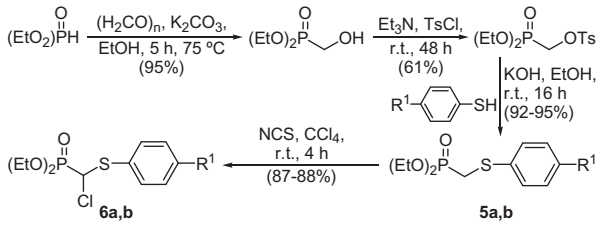


Scheme 1. Proposed synthetic approach toward compounds **1**–**3**.



Scheme 2. Synthesis of the 4-formylpyrazoles **4a**–**c**.



Scheme 3. Synthesis of the thiophosphonate derivatives **5** and **6**.

was employed as the base (entry 3). A better result (71% yield, *trans*/*cis* = 85:15) was observed by the use of *n*-BuLi(entry 4).

The substitution of THF for DME as the solvent gave 71% yield with NaH (entry 5), while the use of *n*-BuLi as base furnished still higher yields of **1a** (87%) and slightly improved the stereoselectivity (*trans*/*cis* = 88:12, entry 6). In addition, it was observed that the use of the ethereal solvents (THF and DME) required reflux conditions for the complete solubilization of the reactants in the reaction medium.

On the other hand, the use of PTC conditions (TEBA-Br and dibenzo-18-crown-6) allowed the reaction to be performed at room temperature, but at the expense of attaining moderate yields and essentially no stereoselectivity (entries 7–10).

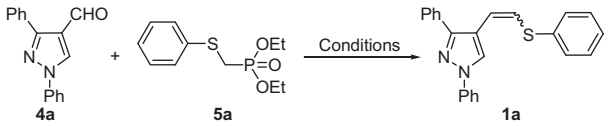
The optimized conditions of the Wittig–Horner reaction with the aldehyde **4a** were employed to synthesize the series of vinyl sulfides **1a**–**l** (Table 2), which were obtained in moderate to good yields, with a high preference for the geometry of the more stable product. The chloro-substituted vinyl sulfides **1g**–**l**, exhibited a slightly lower stereoselectivity (entries 7–12).

In the case of olefins **1a**–**f**, the configuration of the major isomer was found to be *E*, which places apart their bulkier pyrazolyl and arylthio motifs. However, according to the Cahn–Ingold–Prelog priority rules and due to the presence of the chlorine atom, the most stable isomers among compounds **1g**–**l** were the *Z*-alkenes, which also place apart the same bulkier motifs. Therefore, for the sake of convenience, in order to unequivocally identify the isomers and establish structure–reaction outcome relationships, the *cis* and *trans* terms are used to designate the isomers carrying their pyrazolyl and phenylthio moieties on the same and on different sides of the double bond, respectively.

Signal attribution of the vinyl sulfides was confirmed by COSY and NOESY experiments, which enabled the unequivocal identification of the vinylic hydrogens (compounds **1a**–**f**) and the subsequent determination of their coupling constants ($J_{trans} \approx 15$ Hz; $J_{cis} \approx 10$–12 Hz) or the establishment of spatial closeness between substituents in **1g**–**l**. The ^{1}H NMR spectra of the vinyl sulfides **1a**–**f** also revealed an effect of the double bond stereochemistry on H-5 of the pyrazole. For example, the chemical shift of H-5 was δ 8.02 ppm in *trans*-**1a**, while the *cis*-isomer exhibited a resonance at δ 8.47 ppm. The outcome of the reaction agreed with literature precedents for analogous transformations.[17]

Taking into account the importance of the sulfoxide moiety in pharmacological agents, pesticides, and in organic chemistry, the vinyl sulfides **1a**–**l** were oxidized to the corresponding sulfoxides **2a**–**l** with H_2O_2 in AcOH at room temperature (Table 2).[18] For sulfoxides **2a**–**f**, 1.0 equiv of H_2O_2 was enough to achieve good yields (entries 1–6) and *trans*/*cis* ratios (up to 96:4, entries 2 and 3), in 4.5 h. However, the reaction toward the more sterically shielded sulfoxides **2g**–**l** was sluggish, requiring the use of 10 equiv of oxidant and a reaction time of 7 h (entries 7–12). The expected

Table 1
Optimization of the reaction conditions for the Wittig–Horner synthesis of the vinyl sulfide **1a**



Entry N°	Base	Solvent	Temp.	Time (h)	Yield (%)[a]	*E*:*Z*[b]
1	NaH	THF	Reflux	5	53	58:42
2	NaOMe	THF	Reflux	5	25	51:49
3	*t*-BuOK	THF	Reflux	5	Traces	–
4	*n*-BuLi	THF	Reflux	5	71	85:15
5	NaH	DME	Reflux	5	71	67:33
6	*n*-BuLi	DME	Reflux	5	87	88:12
7	NaOH/TEBA-Br[c]	DCM/H_2O	rt	O/N[e]	77	51:49
8	NaOH/TEBA-Br[c]	DCM/H_2O	Reflux	5	78	35:65
9	NaOH/Crown[d]	DCM/H_2O	rt	O/N[e]	67	55:45
10	NaOH/Crown[d]	DCM/H_2O	Reflux	5	64	57:43

[a] Yield of isolated products.
[b] The *trans*/*cis*(*E*/*Z*)ratios were determined by ^{1}H NMR.
[c] TEBA-Br = Benzyltriethylammonium bromide.
[d] Crown = Dibenzo-18-crown-6.
[e] O/N = Overnight.