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Anchimerically Assisted Substitution of a Sulfinyl Function in α-Sulfinylhydrazones by Thiols

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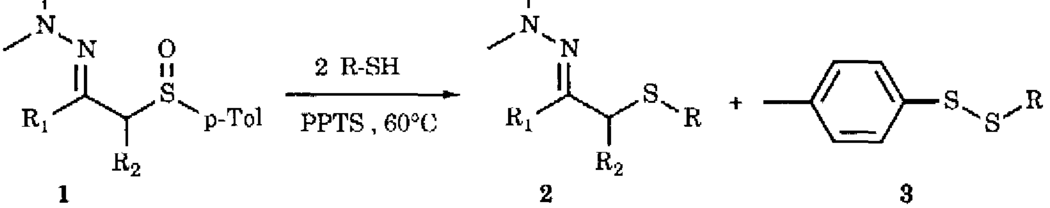
Key words : alpha-sulfinylhydrazone ; thiol ; anchimerically assisted substitution

Abstract : *The reactivity of α-sulfinylhydrazones in the presence of thiols is reported. The reaction occurs probably via an acid catalyzed anchimerically assisted elimination/addition pathway.*

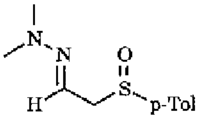
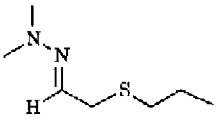
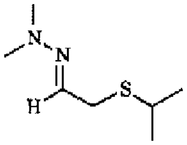
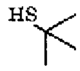
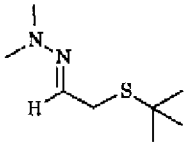
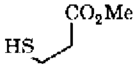
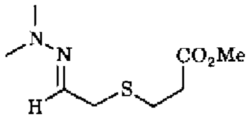
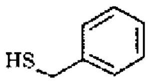
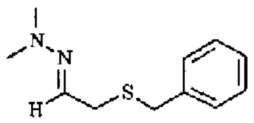
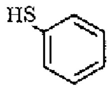
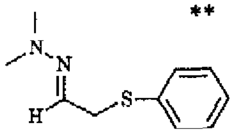
Usually, α-sulfenylated carbonyl compounds are accessible through the S_N2 substitution of an halogen by a thiolate, the attack of an enolate on an activated sulfenyl derivative or using indirect methods via enamines or enol silyl ethers[1]. However, most of these reactions need rather basic or nucleophilic conditions. We report here a new mild reaction to obtain α-sulfenylated aldehydes in weak acidic medium via an α-sulfinylhydrazone.

Recently, we showed that α-sulfinylhydrazones undergo reaction with alcohols[2] to give the corresponding ethers by an acidic catalysis or by methyl iodide initiation. In order to explore the scope and limitations of this reaction we investigated several nucleophiles with various α-sulfinylhydrazones. Carboxylic and sulfonic acids, amines and amides as nucleophiles gave either decomposition products or no reaction at all with α-sulfinylacetaldehyde-dimethylhydrazone (**1a** , R_1=H, R_2=H). Thiols, which are known to be good nucleophiles[3] gave the expected substitution products (Scheme 1) with various yields depending on the nature of both reactants. No reaction occured at room temperature but optimal yields were obtained at temperature between 50 and 60°C, the reaction time being carefully controlled. The reaction proceeds as well in absence of solvent or using anhydrous acetonitrile ; at least two equivalents of thiol are necessary.



Scheme 1 - Reaction of α-sulfinylhydrazones with thiols

Table 1 shows the results obtained by reacting various classes of thiols with compound **1a** (R_1=H, R_2=H).

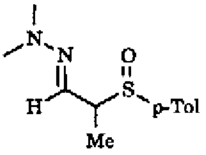
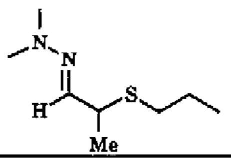
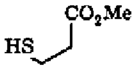
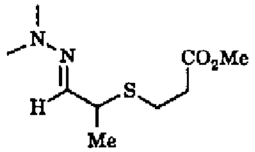
	α-Sulfinyl-hydrazone	Thiol	Product	θ (°C)	Time (h)	Yield (%) *
1	 **1a**			**50**	**2**	**77**
2				**50**	**2**	**71**
3				**50**	**40**	**40**
4				**60**	**3**	**57**
5				**50**	**4**	**75**
6			 **	**60**	**24**	—

* Isolated yield ; ** Expected product

Table 1 - Reaction of α-sulfinylacetaldehyde-dimethylhydrazone with various thiols

Whereas primary and secondary aliphatic thiols (entries 1, 2, 4 and 5) underwent fast reaction with good yields, the tertiary thiol (entry 3) needed longer reaction time and gave only moderate yield. Thiophenol (entry 6) doesn't lead to the expected thioether but mainly to unreacted α-sulfinylhydrazone and some unidentified decomposition products.

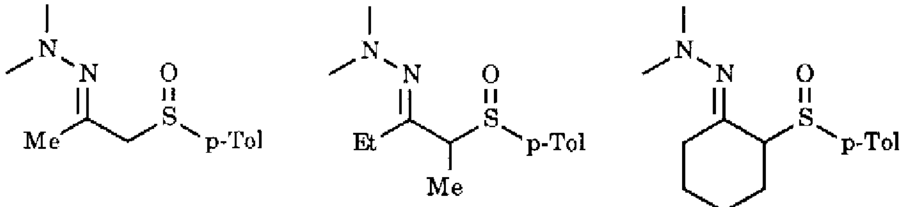
As demonstrated in Table 2, an α-sulfinylhydrazone of an aldehyde bearing an alkyl R_2 substituent, as **1b**, has a reactivity similar to **1a**.

	α-Sulfinyl-hydrazone	**Thiol**	**Product**	**Θ (°C)**	**Time (h)**	**Yield (%) ***
1	 **1b**			50	3	72
2				60	3	54

* Isolated yield

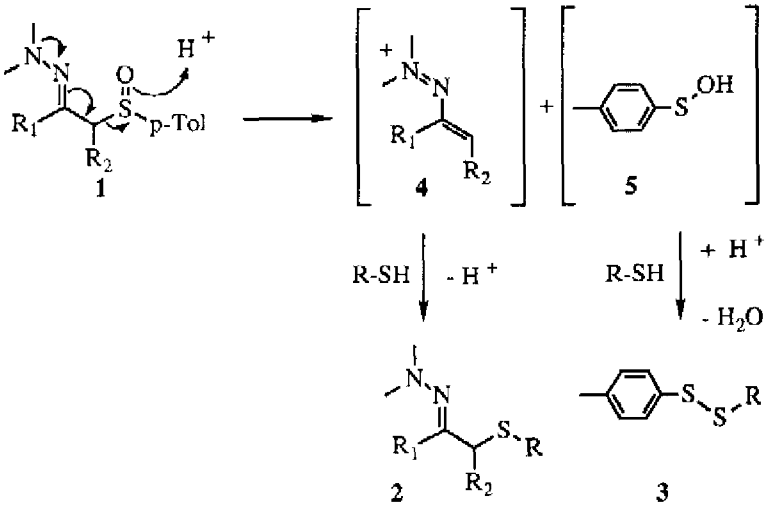
Table 2 - Reaction of α-sulfinylpropionaldehyde-dimethylhydrazone with thiols

Finally, we tried to react three different α-sulfinylhydrazones **1c**, **1d**, **1e** (Scheme 2) derived from ketones (R_1=alkyl) with propanethiol, unfortunately yields were very low (about 5%) and we observed mainly decomposition products.


1c **1d** **1e**

Scheme 2 - α-Sulfinylhydrazones of ketones don't react with thiols

In conclusion, our experiments show that α-sulfinylhydrazones of aldehydes (**1**, R_1=H, R_2=alkyl) react with thiols, probably through an acid catalyzed anchimerically assisted elimination. The vinylic azonium intermediate **4** adds thiol to give the thioether **2**. The sulfenic acid **5** formed during the elimination step is reduced by the excess of thiol in the corresponding mixed disulfide **3** (Scheme 3). All classes of aliphatic thiols react with α-sulfinylhydrazones of aldehydes, but not with α-sulfinylhydrazones of ketones at the opposite of alcohols[2]. The hydrazone can then be easily deprotected to the corresponding aldehyde[5]. We are further exploring these new reactions by trying to apply them to intramolecular cyclizations.



Scheme 3 - Postulated reaction mechanism

Experimental procedure

The α-sulfinylhydrazones are obtained by lithiation of the corresponding hydrazones with nBuLi in THF[4] and further reaction with methyl p-tolylsulfinate at -20°C. The reaction mixture is then allowed to warm up to room temperature in 3 hours. After hydrolysis, the product is purified by silica gel chromatography.

Thiol (5 eq) and α-sulfinylhydrazone (1 eq) are reacted in presence of 0.1 eq of PPTS or Phe_3P,HBr at temperatures between 50 and 60°C, the reaction is monitored by TLC. $NaHCO_3$ hydrolysis, ether extraction and purification by silica gel chromatography (eluent : 90% hexane - 10% ether vol/vol) afforded the mixed disulfide (R_f=0.74 for nPr-S-S-pTol) and the thioether (R_f=0.18 for **1b**).

The corresponding aldehyde is then obtained by deprotection of the hydrazone using $CuCl_2$/phosphate buffer at neutral pH[5].

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