Pergamon

Tetrahedron Letters, Vol. 37, No. 33, pp. 6017-6020, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01264-6

A Novel Route to Enantiomerically Pure Sulfoxides through Displacement of a Carbon Leaving Group

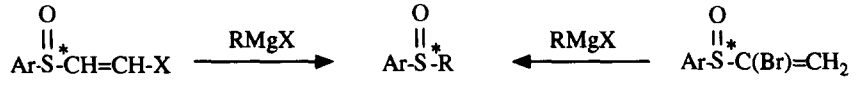
Cosimo Cardellicchio, Antonio Iacuone, Francesco Naso,* and Paolo Tortorella

C.N.R., *Centro di Studio sulle Metodologie Innovative di Sintesi Organiche*, Dipartimento di Chimica, via Amendola 173, 70126 Bari, Italy

Abstract. Enantiomerically pure sulfoxides were produced by reaction of dimethyl (S)-p-tolylsulfinylmethylphosphonate with the suitable Grignard reagents. Yields up to 75% were obtained.

In connection with work on new synthetic methodologies leading to chiral products, we have reported a novel enantiospecific approach to chiral sulfoxides.[1] This was based upon the reaction of chiral halovinyl derivatives with a Grignard reagent (Scheme).

Scheme



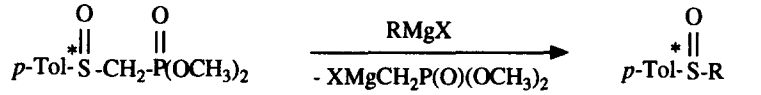
A similar approach was reported also for phosphine oxides[2] according to the following equation:

Both the above processes were found to occur with inversion of configuration. It is worth noting that other organometallic reagents (*e.g.* organocuprates or organolithium compounds) reacted with the above substrates in different ways.

In view of the interesting results obtained using the halovinyl moiety, we considered of interest to evaluate the use of other readily available compounds possessing a potential carbon leaving group in their structure. Therefore, we turned our attention toward dimethyl (*S*)-*p*-tolylsulfinylmethylphosphonate **1**.[3-4] This compound had been used by other workers[3-5] and by us[6] in Horner-Wadsworth-Emmons (HWE) procedures leading to optically active vinyl sulfoxides. In these olefination processes, the carbanion necessary for the reaction with carbonyl compounds was obtained using a variety of bases (including *n*-butyllithium).

Now we wish to report that, when a Grignard reagent is used as a base, it becomes possible to direct the reaction toward the displacement of the anion of dimethyl methylphosphonate with formation of the corresponding sulfoxides (see Table).

Table: Reaction of Dimethyl (*S*)-*p*-Tolylsulfinylmethylphosphonate with Grignard Reagents



(*S*)-**1** (*S*)-**2 - 6**

Entry	R	Product	Solvent[a]	RMgX/1 ratio	Yield (%)[b]	Recovered **1**(%)[b]	e.e.(%)[c]
1	Ph	**2**	Et_2O	1.5 : 1	49	--[d]	--[d]
2	Ph	**2**	THF	1.5 : 1	62	--[d]	>98
3	Ph	**2**	THF	2 : 1	46	38	--[d]
4	Ph	**2**	Benzene	1.5 : 1	75	19	>98
5	Ph	**2**	Benzene	2 : 1	60	--[d]	--[d]
6	*i*-Pr	**3**	THF	1.5 : 1	39	--[d]	>98
7	*n*-Pr	**4**	THF	1.5 : 1	41	--[d]	>98
8	*i*-Pr	**3**	Benzene	1.5 : 1	51	48	98
9	*i*-Pr	**3**	Benzene	2 : 1	45	--[d]	--[d]
10	*n*-Pr	**4**	Benzene	1.5 : 1	54	42	>98
11	Et	**5**	Benzene	1.5 : 1	61	38	>98
12	Me	**6**	Benzene	1.5 : 1	50	49	>98

(a) Reaction solvent. Grignard reagents always prepared in THF. (b) Yields refer to products purified by column chromatography. (c) e.e. values were determined by HPLC[7] and refer to compounds purified by column chromatography.(d) Not determined.

The reaction is enantiospecific, with complete inversion of configuration at the sulphur atom.[7] After the neutralization and the usual work-up, the novel carbon leaving group was recovered as dimethyl methylphosphonate. Furthermore, the reaction did not reach completeness, thus suggesting a competition between metalation and attack at the sulphur atom. However, the part of **1** which did not undergo carbon-sulphur bond formation was easily recovered.

The data in the Table show that the solvent has a crucial role. Better results were obtained using THF or benzene (entries 2, 4), rather than diethyl ether (entry 1). Furthermore, under the same reaction conditions,

better isolated yields were obtained by using benzene (entries 4, 8 and 10) instead of THF (entries 2, 6 and 7). The best ratio between the Grignard reagent and the substrate was found to be 1.5:1 (entries 2, 4, 8). When a lower ratio was used, higher quantities of unreacted substrate were recovered, whereas a higher ratio (*i.e.* 2:1) caused the competitive ligand exchange reaction[8] between the product and the Grignard reagent, thus leading to a decrease of the yields (entries 3, 5 and 9).

At least within certain limits, proper reaction conditions could tune the amount of the products deriving from the cleavage or from the metalation reaction, as shown by the variable quantity of **1** recovered (see Table). Furthermore, it was possible to use again the recovered substrate in displacement reactions, without any significant decrease of the enantiomeric purity of the synthesized sulfoxides.

In conclusion, the procedure here reported represents a novel route to enantiomerically pure sulfoxides.[9] Obviously, the validity of the method hinges upon the methods available for the preparation of **1**. In this respect, it is worth noting that such a compound can be prepared not only from resolved menthyl sulfinate, but also from the corresponding monomethyl ester (*i.e.* methyl *p*-tolylsulfinylmethylphosphonic acid) which in turn can be readily obtained by optical resolution of its quininium salt.[3] Therefore, as a whole, this work appears to offer an alternative to the most classical route leading to sulfoxides (*i.e.* the Andersen procedure[5]).

Synthesis of phenyl *p*-tolyl sulfoxide 2.

1.6 mL of a 0.94 N solution of phenylmagnesium bromide in THF, under N_2, was added dropwise to a stirred solution of 0.257 g (0.98 mmol) of **1** in 7 mL of benzene, under N_2. After 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted three times with ethyl acetate. The combined organic extracts were washed with water, dried (Na_2SO_4), and then the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, eluents ethyl acetate/petroleum ether 3:7) to give 0.159 g (75%) of phenyl *p*-tolyl sulfoxide; mp=92-93° (*n*-hexane); $[\alpha]_D$=-21.2° (c=2, acetone).[16] 0.049 g (19%) of phosphonate **1** were also recovered.

Acknowledgement: Work supported in part by Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome.

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7. An analytical Chiralcel OD column was used to confirm the e.e. value of the chiral synthesized *p*-tolyl sulfoxides. The following conditions were optimized on racemic products, obtaining α values (separation factors) equal to *ca* 1.1-1.2; solvent: *n*-hexane/*i*-propanol 95/5; for sulfoxides **2-3**: flow rate 0.5 mL/min; for sulfoxides **4-6**: flow rate 1 mL/min.

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(*Received in UK* 31 *May* 1996; *revised* 24 *June* 1996; *accepted* 28 *June* 1996)