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Prenyl and geranyl phenyl sulfone, a new carbon nucleophile for Mitsunobu-type alkylation

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Abstract—Cyanomethylenetrimethylphosphorane (CMMP), a new Mitsunobu reagent developed recently by the authors, mediated the alkylation of prenyl and geranyl phenyl sulfone with primary and secondary alcohols quite efficiently. Utilizing geranyl phenyl sulfone, norfaranal, an analog of the unique trail pheromone produced by Pharaoh's ant, was synthesized in a short number of steps. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, we demonstrated that cyanomethylenetrimethylphosphorane (CMMP)¹ mediated the *C*-alkylation of some doubly activated methylene and methine compounds, such as phenylsulfonylacetonitrile (**1a**), 2-(phenylsulfonyl)hexanenitrile (**1b**), (methylthiomethyl)tolylsulfone (**2**), and arylmethyl phenyl sulfones **3**, in a Mitsunobu-type reaction (Scheme 1).² The traditional Mitsunobu reagent (DEAD–PPh₃) barely promotes the reaction of these carbon nucleophiles with alcohols.³ Therefore, CMMP augments the synthetic value of the Mitsunobu reaction and it provides now a very attractive versatile methodology for C–C bond formation. In our continuing efforts to know the scope and limitations of the synthetic value of this mediator, we found that allylic phenyl sulfones **5** and **6**⁴ were alkylated effectively. In this paper, we describe the results of these reactions and an application to a synthesis of (+)-norfaranal [(+)-(7)],⁵ which is an analog of

$$R-OH + Y \xrightarrow{SO_2R''} (CMMP) \xrightarrow{Y} \xrightarrow{SO_2R''} R = Ph$$

$$1a: Y = CN, R' = H, R'' = Ph$$

$$1b: Y = CN, R' = butyl, R'' = Ph$$

$$2: Y = SMe, R' = H, R'' = p-Tol.$$

$$3: Y = Ar, R' = H, R'' = Ph$$

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. . .

Scheme 1.

Ph
$$OH + SO_2Ph \xrightarrow{CMMP (1.5 equiv.)}{Tol., 100°C, 24 h} + SO_2Ph + SO_2Ph$$

Scheme 2.

Keywords: Mitsunobu reactions; phosphorane; sulfones; pheromone.

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(+)-faranal,^{6,7} the unique trail pheromone produced by Pharaoh's ant (*Monomorium pharanis*, L.).

With 1.5 equiv. of CMMP at 100°C in toluene,⁸ methallyl phenyl sulfone (4) was converted to the benzylated compound 8 in 51% yield (Scheme 2). However, a considerable amount of vinyl sulfones 9 and 10 was also obtained. Since the tendency of double bond migration was dominated by the thermodynamical stability of olefin, the reactions of trisubstituted allylic sulfones 5 and 6, more stable olefins, were carried out using alcohols of different structure types. The results are listed in the Table 1.

The alkylation of sulfones **5** and **6** proceeded smoothly at 100°C to afford the corresponding product without olefin migration according to expectation. For the reaction of both sulfones, a 1:3 mixture of hexane–benzene was the best solvent. 1,2-Dimethoxyethane (DME) could also be used for the reaction of **6**. Although a higher temperature was needed (120°C) for the reaction of 2-octanol, a secondary alcohol, all types of alcohols tested condensed with **5** and **6** quite efficiently.

In order to demonstrate the usefulness of the reaction, norfaranal was synthesized. The mono-MPM ether of (2S,3S)-2,3-butanediol (11) was reacted with $1a^9$ in the

presence of CMMP to afford the nitrile 12 satisfactorily with Walden inversion of the carbinyl carbon on 11 (Scheme 3). The acetal-alcohol 13 was obtained by desulfurization of 12 with SmI₂ followed by reduction of the nitrile with DIBAL, protection of the resulting formyl group, and removal of the MPM group. The usual Mitsunobu reaction with benzoic acid and subsequent hydrolysis was employed to invert the hydroxy group on 13 to give the alcohol 14. The geranyl sulfone 6 (3.0 equiv.) was subjected to the present CMMP (3.0) equiv.) alkylation with the alcohol 14 to give the sulfone 15. Palladium-catalyzed reaction (10 mol% of PdCl₂(dppp) and 4.0 equiv. of LiHBEt₃)¹⁰ induced the cleavage of the C-S bond to give acetal 16. Quick hydrolysis (30 min) of the acetal with 3 equiv. of *p*-TsOH in THF–H₂O led to (+)-norfaranal [(+)-7] as a colorless oil, $[\alpha]_{D}^{22}+21.9$ (c 1.00, CHCl₃), in addition to 21% of the starting material being recovered. Physical properties of (+)-7 are well compared with those in the literature^{7c} $[\alpha]_{D}^{22}$ +17.5 (c 4.46, CHCl₃)].

Thus, we have demonstrated that trisubstituted allylic phenyl sulfones of pK_a up to 22.5 can be utilized in the CMMP mediated Mitsunobu reaction. The C–C bond formation reaction, being much more versatile than ever, should find much wider application in organic syntheses.

Table 1. Alkylation of allylic sulfones (% yield)

		P	CMMP (1.5 equiv.)	R'
R'-OH	+	SO ₂ Ph	solv., 100°C, 24 h	R SO ₂ Ph
		(1.5 equiv.)		
		5 : R = H		
		6 : $R = Me_2C=CHCH_2$	-	

	5	6		
R'-OH	in Hex. / PhH (1 / 3)	in Hex. / PhH (1 / 3)	in DME	
Ph ^{OH}	98	89	87	
М	89	87	86	
ОН	93	92	100	
ⁿ C ₁₆ H ₃₃ OH	96	89		
HexOH	78 ^a	82	76 ^a	

a: The reaction was carried out at 120°C .



Scheme 3.

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- 8. In a typical experiment, an Ace pressure tube (max. 200 psi) was used as a sealed reactor at higher temperature. CMMP ($1.5 \sim 3.0 \text{ mmol}$) was added to a dry solvent solution of an alcohol (1 mmol) and allylic sulfone (1.5 mmol) with stirring under argon atmosphere. The mixture was heating at $100 \sim 120^{\circ}$ C for 24 h in the sealed tube. The product was purified by silica gel column chromatography after evaporation of the solvent in vacuo. All new compounds were characterized by IR, 1H-NMR, MS, analysis or High-MS.
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