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Arylmethyl phenyl sulfones, a new carbon nucleophile for Mitsunobu-type alkylation

Tetsuto Tsunoda,* Kaori Uemoto, Tomoko Ohtani, Hiroto Kaku and Shô Itô

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima 770-8514, Japan

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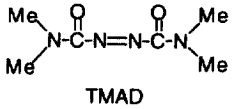
Abstract

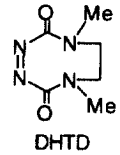
Cyanomethylenetrimethylphosphorane (CMMP), a new Mitsunobu reagent developed recently by the authors, mediated the alkylation of arylmethyl phenyl sulfones with primary and secondary alcohols quite efficiently. Utilizing 3-((phenylsulfonyl)methyl)pyridine, theonelladine D, a unique pyridine alkaloid, was synthesized in excellent yield.

Keywords: Mitsunobu reactions; phosphorane; sulfones; alkaloids.

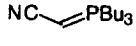
Recently, we demonstrated that our new reagents, TMAD-PBu_3,[1] DHTD-PBu_3,[2] CMBP[3] and cyanomethylenetrimethylphosphorane (CMMP)[4] mediated the *C*-alkylation of some doubly activated methylene and methine compounds, such as phenylsulfonylacetonitrile (**1a**), 2-(phenylsulfonyl)hexanenitrile (**1b**), and (methylthiomethyl)tolylsulfone (**2**) under the Mitsunobu conditions (Scheme 1).† Furthermore, comparative studies of these reactions allowed us to estimate the general reactivity of the mediators as TMAD-PBu_3<DHTD-PBu_3<CMBP<CMMP for C–C bond formation.



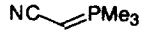
TMAD



DHTD



CMBP



CMMP

The recognition of these powerful mediators reinforces the synthetic value of the Mitsunobu reaction in addition to its well-known advantage of requiring no prerequisite activation of the alcohol and proceeding under neutral conditions, and thus it is now a very attractive versatile methodology for C–C bond formation. In our continued effort to get a clear view of the synthetic value of these mediators, we found that arylmethyl phenyl sulfones **3**, quite weakly activated carbon nucleophiles, were alkylated effectively.

* Corresponding author. Fax: +81 88 655 3051; e-mail: tsunoda@ph.bunri-u.ac.jp

† New Mitsunobu reagents: See the preceding paper by Tetsuto Tsunoda, Kaori Uemoto, Chisato Nagino, Megumi Kawamura, Hiroto Kaku, and Shô Itô, for preparation.

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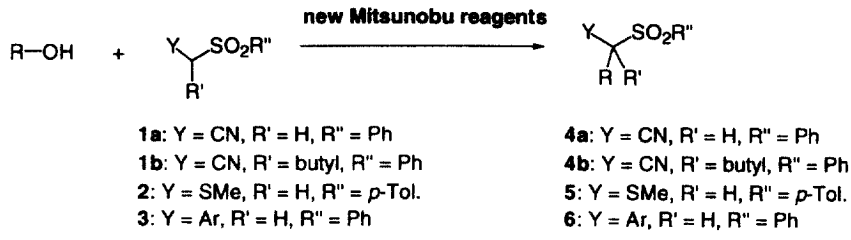
PII: S0040-4039(99)01510-5



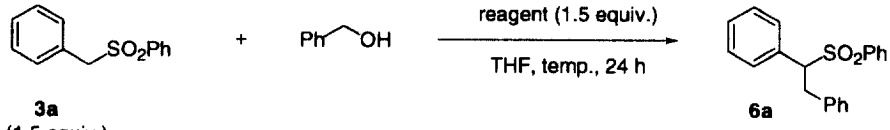
1a: Y = CN, R' = H, R" = Ph
1b: Y = CN, R' = butyl, R" = Ph
2: Y = SMe, R' = H, R" = *p*-Tol.
3: Y = Ar, R' = H, R" = Ph

4a: Y = CN, R' = H, R" = Ph
4b: Y = CN, R' = butyl, R" = Ph
5: Y = SMe, R' = H, R" = *p*-Tol.
6: Y = Ar, R' = H, R" = Ph

Scheme 1.

In this paper, we describe the results of the reactions and its application to a synthesis of theonelladine D (**7**), a unique pyridine alkaloid isolated from the Okinawan marine sponge *Theonella swinhoei*.[5,6]

Benzyl phenyl sulfone (**3a**),[7] pK_a=23.4 in DMSO,[8] was benzylated smoothly at 80°C in THF to give 1,2-diphenylethyl phenyl sulfone (**6a**) in 70% and 90% yield, respectively,[‡] in the presence of the phosphorane type reagents, CMBP and CMMP, though azo reagents hardly mediated the reaction (7% yield with DHTD-PBu$_3$) (Scheme 2), thus reconfirming the reactivity order described above.



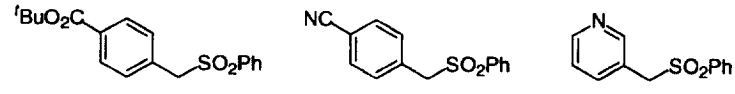
3a
(1.5 equiv.)

6a

Scheme 2.

The reactions of 4-*t*-butoxycarbonylphenylmethyl phenyl sulfone (**3b**),[§] 4-cyanophenylmethyl phenyl sulfone (**3c**),[10] pK_a=18.5 in DMSO,[11] and 3-((phenylsulfonyl)methyl)pyridine (**3d**),[12] pK_a=16.7 in DMSO[8] were also carried out using alcohols of different structure types. The results are listed in Table 1.

New Carbon Nucleophiles



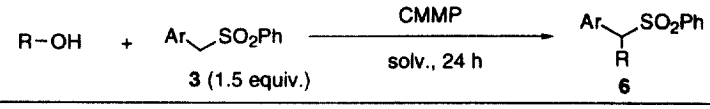
3b **3c** **3d**

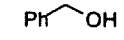
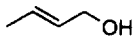
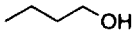
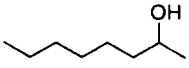
The factors influencing the yield were examined for the reaction of the sulfone **3b** with butanol. With 1.5 equivalents of CMMP, the standard ratio of the mediator, the alkylation proceeded slowly at 80°C in THF giving the product in only 59% yield after 24 h, the rest being the starting materials. Although an extended reaction period (48 h) improved the yield (95%), the reaction was accelerated by doubling (3.0 equiv.) the amount of CMMP to complete the reaction after 24 h. All the other alkylations of **3b** and **3c** were therefore performed under the latter conditions to give satisfactory results with all types of alcohols examined. For the reactions of **3d**, however, 1.5 equivalents of CMMP was quite sufficient at somewhat higher temperature (100°C), but the reaction of 2-octanol, a secondary alcohol, needed a still higher temperature (120°C).

[‡] Experimental conditions: In a typical experiment, an Ace pressure tube (max. 200 psi) was used as a sealed reactor at higher temperature. CMMP (1.5–3.0 mmol) was added to a dry solvent solution of an alcohol (1 mmol) and arylmethyl sulfone (1.5 mmol) with stirring under argon atmosphere. The mixture was heating at 80–120°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, ^{1}H NMR, MS, analysis or High-MS.

[§] Preparation of **3b**: Hydrolysis of 4-methoxycarbonylphenylmethyl phenyl sulfone[9] followed by treatment with oxalyl chloride afforded the acid chloride, which reacted with lithium *t*-butoxide to give **3b**.

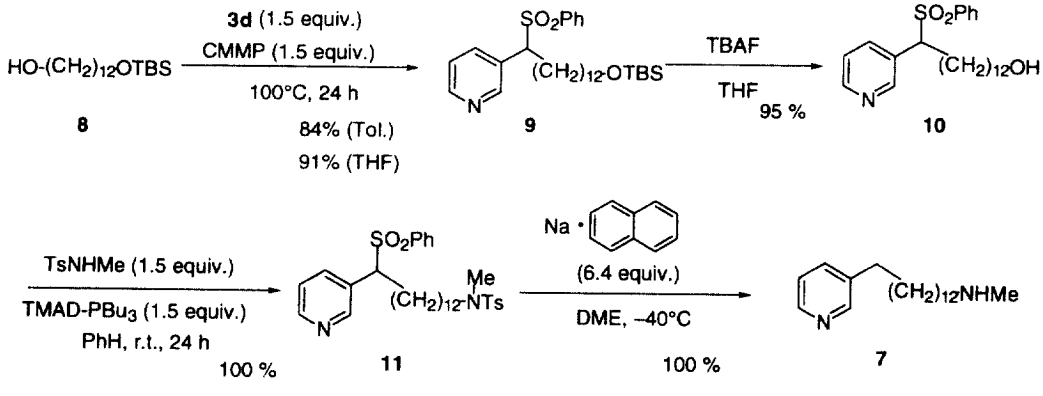
Table 1
Alkylation of arylmethylsulfones (% yield)



R-OH	Carbon Nucleophile					
	3b [a]		3c [a]		3d [b]	
	in THF	in Tol.	in THF	in Tol.	in THF	in Tol.
	92	83	95	100	94	92
	86	85	81	86	85	86
	59 [c] 95 [d] 100	88	99	100	99	93
	91	92	100	100	100 [e]	87 [e]

The reactions were carried out under the following conditions. a: at 80°C with 3.0 equiv. of CMMP for 24 h. b: at 100°C with 1.5 equiv. of CMMP for 24 h. c: at 80°C with1.5 equiv. of CMMP for 24 h. d: at 80°C with 1.5 equiv. of CMMP for 48 h. e: at 120°C with 1.5 equiv. of CMMP for 24 h.

In order to demonstrate the usefulness of the reaction, a synthesis of theonelladine D (**7**) was carried out.[5,6] The sulfone **3d** was subjected to the present CMMP alkylation with 1,12-dodecanediol monosilyl ether (**8**) to give the silyl ether **9** (Scheme 3). Desilylation of **9** (95% yield) and subsequent Mitsunobu reaction with *N*-methyltosylamide in the presence of TMAD-PBu_3 afforded the amide **11** in quantitative yield.[1] Treatment of **11** with sodium naphtalenide at –40°C in DME induced the simultaneous cleavage of both the S–N[13] and S–C bonds to give **7**, a colorless oil, in quantitative yield.



Scheme 3.

Thus, we have demonstrated that arylmethyl phenyl sulfones of pK_a up to 23.5 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.

Acknowledgements

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