Pergamon

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Mitsunobu-type Alkylation of *p*-Toluenesulfonamide. A Convenient New Route to Primary and Secondary Amines

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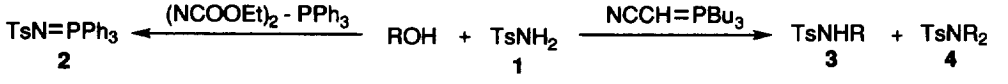
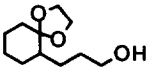
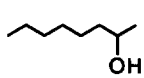
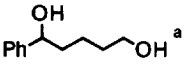
Abstract: *p*-Toluenesulfonamide, which is known to form phosphine imides under Mitsunobu conditions, was shown to be alkylated in the presence of cyanomethylenetributylphsphorane to give *N*-substituted sulfonamides in excellent yields. The reaction can be applied to the synthesis of symmetrical and unsymmetrical *N,N*-disubstituted amides. When coupled with the desulfurization reactions, the reaction provides a new versatile synthetic route to primary and secondary amines from ammonia. Copyright © 1996 Elsevier Science Ltd

N-Substituted sulfonamides have successfully been *N*-alkylated under the traditional Mitsunobu conditions (alcohols, DEAD and PPh_3).[1] The reaction, when coupled with the known methods of desulfurization,[2] provides an excellent route to secondary amines. The method, however, can not be applied to the synthesis of primary amines, because the starting amides, e.g. *p*-toluenesulfonamide (**1**), react with PPh_3 to form triphenylphosphine tosylimide **2** under the reaction conditions.[3] The same is true with our new azodicarboxamide reagents,[4] e.g. TMAD-PBu_3. By contrast, the alkylation was now found to proceed smoothly with cyanomethylenetributylphosphorane (CMBP), one of our phosphorane reagents,[5] to give the desired *N*-substituted sulfonamides **3** in excellent yields, establishing a new versatile synthetic method to primary amines. The results are described herein.



The experimental procedure is as follows. While the reactions at higher temperatures followed the general procedure described earlier,[5] those at room temperature were performed by adding CMBP (1.5 mmol) to a dry benzene (5 m*L*) solution of an alcohol (1 mmol) and **1** (1.5 mmol) under argon atmosphere, and stirring for 24 h. The products were isolated by silica-gel column chromatography after evaporation of the solvent *in vacuo*. The results are listed in Table.

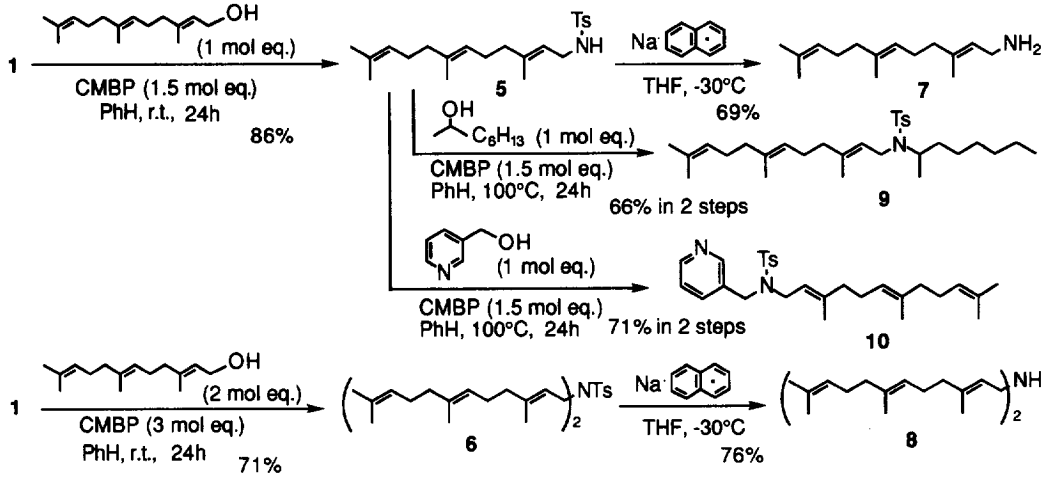
Table. CMBP-Mediated reaction of *p*-toluenesulfonamide with alcohols

R-OH	Temp. (°C)	% Yield 3	% Yield 4	R-OH	Temp. (°C)	% Yield 3	% Yield 4
	r.t.	93	0		r.t.	70	22
	r.t.	88	0		r.t.	78	12
	80	89	0		100	0	46 (39)[b]

a: Three molar equivalents of CMBP were used. b: The figure in parentheses is the yield of α-phenyltetrahydropyran, the simple dehydrocyclization product of the diol

From Table the following can be seen: 1) Primary alcohols give the alkylation products in satisfactory yields at room temperature, but 2) benzylic and allylic alcohols are too reactive under the same conditions, forming double alkylation products to some extent. 3) The reaction of secondary alcohols needs higher temperatures to proceed, and 4) the double alkylation of **1** with a diol in the presence of 3 molar equivalents of CMBP suffered from the competing dehydrocyclization of the diol. When coupled with the known desulfurization reactions,[2] the alkylation reaction constitutes a new versatile methodology for the synthesis of primary amines.

Being equivalent to the alkylation of ammonia, the reaction also provides a convenient new route to secondary amines. Thus, in addition to those implied from Table, the reaction of **1** and farnesol furnished mono- **5** or disubstituted tosylamide **6** in good yields, depending on the amounts of CMBP and farnesol used. Both **5** and **6** were reduced to the corresponding amines **7** and **8**, respectively. For the synthesis of unsymmetrical secondary amines, the second alcohol and CMBP were added to the reaction mixture of the first alkylation and the desired *N,N*-disubstituted tosylamides **9** and **10** were obtained in one pot. Thus, the method was demonstrated to be applicable to the synthesis of unsymmetrical secondary amines as well as of symmetrical amines.[6]



REFERENCES AND NOTES

1. Reviews: Hughes, D. L. The Mitsunobu Reactions, in *Organic Reactions*; Beak, P. *et al.* Eds; John Wiley & Sons, Inc.: New York, **1992**, Vol. 42, pp 335-656. Recent works: e.g. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373-6374. Bell, K.-E.; Knight, D.-W.; Gravestock, M.-B. *Tetrahedron Lett.* **1995**, *36*, 8681-8684, and the references cited therein.
2. *Interal.*, Na / naphthalene: Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311-5312. Na / ammonia: Kovacs, J.; Ghatak, U. R. *J. Org. Chem.* **1966**, *31*, 119-121.
3. Bittner, S.; Assaf, Y.; Krief, P.; Pomerantz, M.; Ziemnicka, B.T.; Smith, C. G. *J. Org. Chem.* **1985**, *50*, 1712-1718.
4. Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639-1642. Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chemistry Lett.* **1994**, 539-542. Itô, S.; Tsunoda, T. *Pure & Appl. Chem.* **1994**, *66*, 2071-2074. Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Itô, S. *Tetrahedron Lett.* **1995**, *36*, 2531-2534.
5. Tsunoda, T.; Ozaki, F.; Itô, S. *Tetrahedron Lett.* **1994**, *35*, 5081-5082.
6. The amine **8** is one of the squalene synthetase inhibitors, and **10** is the tosyl derivative of another. Cf. Prashad, M.; Kathawala, F. J.; Scallen, T. *J. Med. Chem.* **1993**, *36*, 1501-1504.

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