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New Mitsunobu reagents in the C–C bond formation. Application to natural product synthesis*

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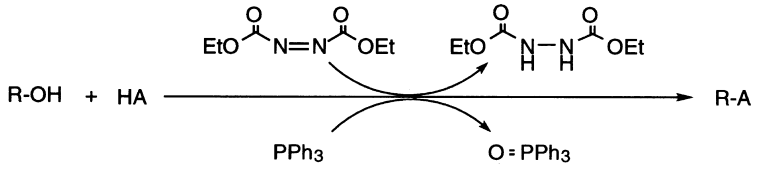
Abstract: Two types of new mediators were developed to replace DEAD-TPP in Mitsunobu reaction. One is *N,N,N′,N′*-tetrasubstituted azodicarboxamide (e.g. TMAD or DHTD)-TBP system, and the other cyanomethylenetrialkylphosphoranes (e.g. CMBP and CMMP). While all of them are more effective than DEAD-TPP in the *N*- and *C*-alkylation with primary alcohols, DHTD and the phosphorane reagents are excellent mediators for the reaction with secondary alcohols. Furthermore, the phosphoranes, especially CMMP, were found to be much more versatile in *C*-alkylation: they mediate the reaction of acids of p$K_a \cong 23$ (MT sulfone, benzyl phenyl sulfone, geranyl phenyl sulfone, etc.). Utilizing the *C*-alkylation reaction with these new mediators, some natural products or their analogs, including pheromones and pyridine alkaloids, were synthesized.

INTRODUCTION

The Mitsunobu reaction is a versatile alkylation reaction of various Brønsted-Lowry acids (HA) by an alcohol, proceeding smoothly in neutral media and normally at a room temperature in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) (Scheme 1) [1].



Scheme 1

The merit of this unique reaction, besides the variety of the acids applicable, is that the alcohol is utilized without any prerequisite activation, unlike many other alkylation reactions. This is particularly appreciated when the alcohol is allylic or has a chiral center at its α-carbon, since undesired side reactions in the activation process can be avoided.

However, the reaction has a serious drawback; the acid has to have a pK_a less than 10 in order to achieve a synthetically meaningful alkylation. In order to overcome the drawback, we have been trying for some years to develop more efficient mediators than DEAD-TPP. In this report, we present the result of our search for new versatile reagents and describe the possibility of their application to the natural product synthesis.

Starting with close examination of the generally accepted mechanism of the Mitsunobu reaction [1], we developed *N,N,N′,N′*-tetrasubstituted azodicarboxamides, exemplified by TMAD and DHTD, shown below, to be used along with tributylphosphine (TBP) in benzene rather than TPP in THF [2–4].

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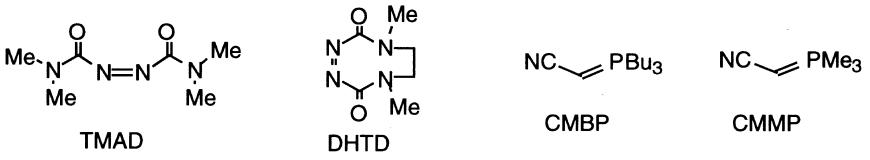
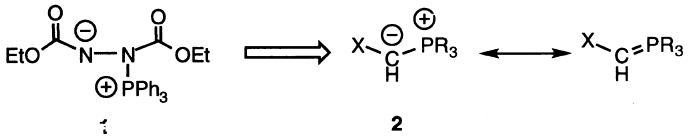
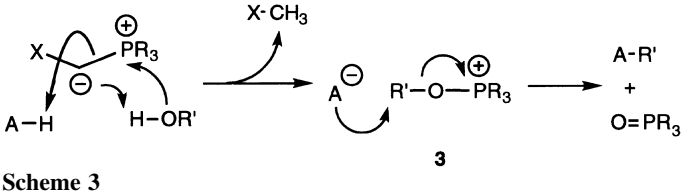


Furthermore, the structural similarity between a proposed intermediate **1** in Mitsunobu reaction and phosphonium ylides **2** implied that the latter would also form, by reacting with an acid and an alcohol, the alkoxyphosphonium ion [3], which would then be attacked by the acid anion to give the final product (Schemes 2 and 3). The investigation resulted in the discovery of another type of the mediators, the stabilized trialkylphosphoranes (e.g. CMBP and CMMP), also to be used generally in benzene at an elevated temperature [5–7].



Scheme 2

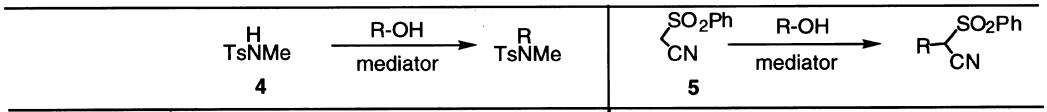


Scheme 3

EFFICIENCY OF NEW MEDIATORS

The efficiency of the new mediators for the reactions of weaker acids was evaluated using that of **4** ($pK_a = 11.7$) and **5** ($pK_a = 12.0$) toward various types of alcohols. The results are listed in the Table 1 [3–7].

Table 1 *N*- and *C*-alkylation (% yield) of **4** and **5**[1]



mediator	DEAD-TPP	TMAD-TBP	DHTD-TBP	CMBP		CMMP	TMAD-TBP	DHTD-TBP	CMBP		CMMP
solvent	THF	PhH	PhH	PhH		PhH	PhH	PhH	PhH		PhH
R-OH temp.(°C)	r.t.	r.t.	r.t.	r.t.	100	r.t.	r.t.	r.t.	r.t.	100	100
C_4H_9OH	65	100	100	99	100	—	63	97	66	96	—
$PhCH_2OH$	66	99	97	81	100	—	59 (3)[2]	46 (51)	75 (21)	72 (28)	—
OH	51	96	97	83	100	—	64 (16)	52 (22)	76	89	—
C_6H_{13} OH	53	40	85	60	89	98	23	67	4	66	94

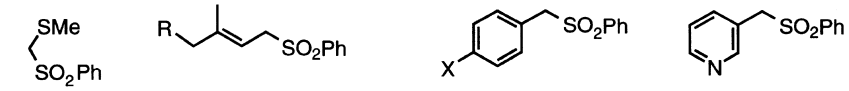
[1]The ratio of the reactants: ROH:acid:mediator = 1:1.5:1.5. Reaction period: 24 h.
[2]The figures in parentheses are the % yield of dialkylation products.

The Table 1 discloses: (a) all new mediators are by far more efficient than DEAD-TPP in the *N*-alkylation with primary alcohols, (b) DHTD-TBP is the only satisfactory azodicarboxamide for the reaction with secondary alcohols, (c) CMBP, somewhat less active at a room temperature, is quite

satisfactory at 100 °C with all alcohols tested, and (d) CMMP is more efficient than CMBP as it mediates the reaction well with secondary alcohols even at a room temperature, (e) the *C*-alkylation follows the same tendency as the *N*-alkylation, CMMP being the most active, and (f) for the reactions of the alcohols having α-electrons, further alkylation occurs to give the corresponding dialkyl compounds.

REACTION OF PHOSPHORANES WITH WEAKER ACIDS

Since some of the new mediators were found to be quite effective for the *C*-alkylation of weak acids of $pK_a \cong 12$, and the monoalkylation products, which are presumably weaker acids than the corresponding starting materials, were alkylated further (Table 1), we tried the reactions of the following phenyl or tosyl sulfones **6**–**11** of much larger pK_as [6].



6 $pK_a = 23.4$

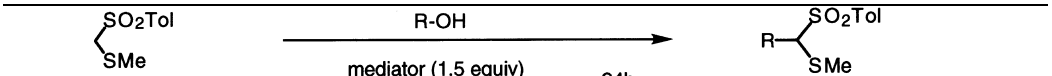
7 R = H
8 R = prenyl
pK_a = ~23 for both **7** and **8**

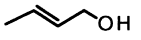
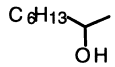
9 X = H $pK_a = 23.4$
10 X = CN $pK_a = 18.5$

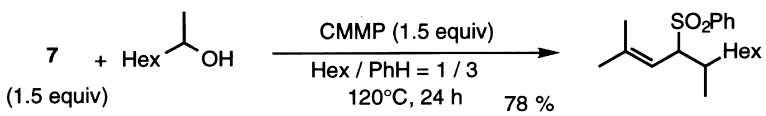
11 $pK_a = 16.7$

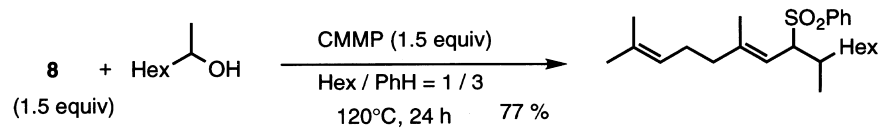
While all of the azodicarboxamides were inactive, the phosphoranes especially CMMP were found to be quite efficient for all the *C*-alkylations examined. Some of the results are shown in the Table 2 and the following schemes.

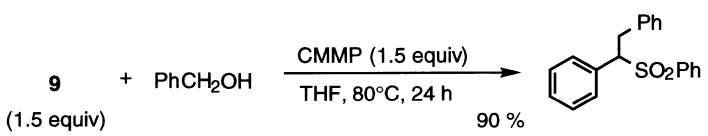
Table 2 Reaction (% yield) of MT sulfone **6**



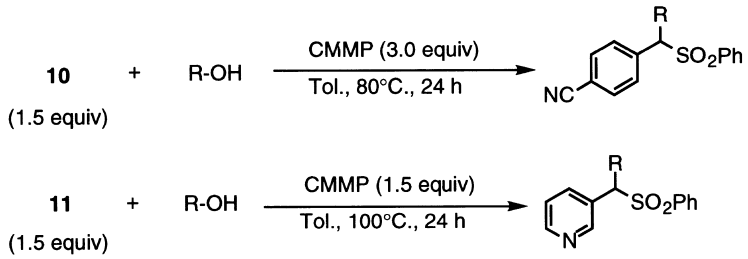
R—OH	mediator	DEAD-TPP	TMAD-TBP	DHTD-TBP	CMBP			CMMP
	solvent	THF	PhH	PhH		PhH		PhH
	temp. (°C)	r.t.	r.t.	r.t.	100°C	120°C	150°C	100°C
C_4H_9OH		—	—	0	85	94	—	—
$PhCH_2OH$		0	0	1.6	40*	41*	—	—
		—	—	1.3	50	68	—	—
		0	0	0	44	71	88	88







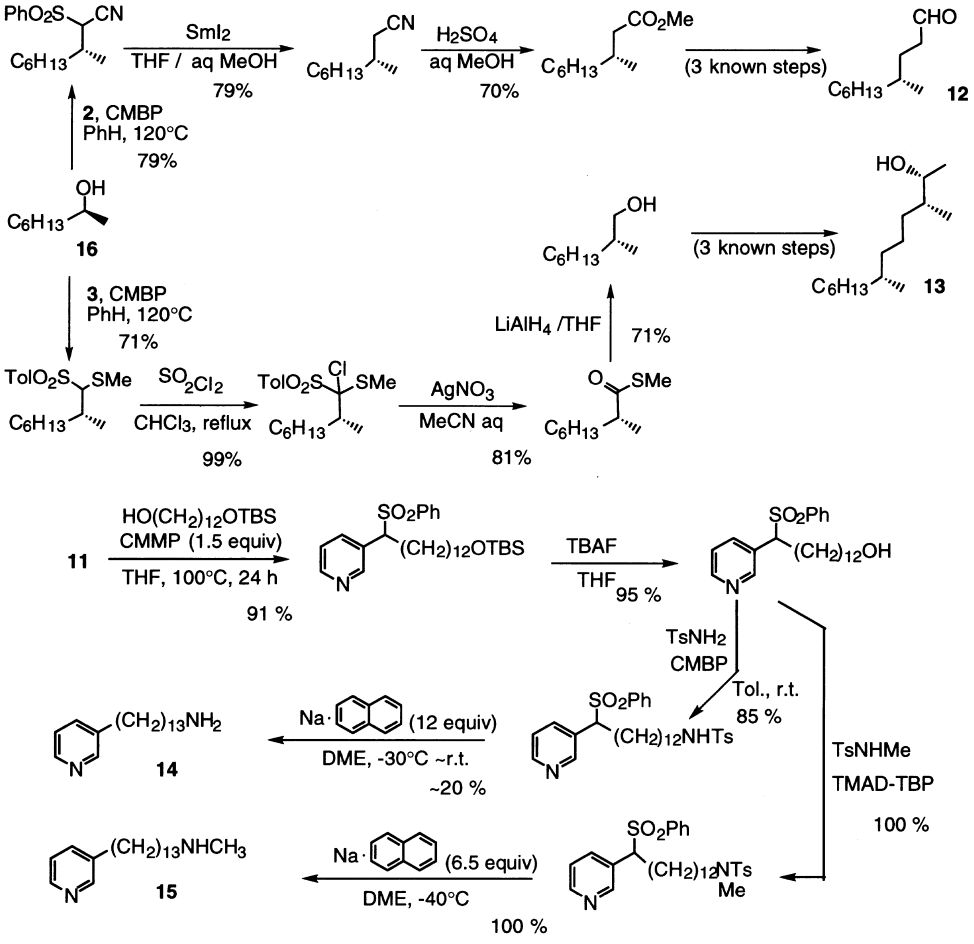
Cf. DHTD-TBP (r.t.) 7 %
CMBP (80°C) 70 %



R-OH	Starting Mat. 10	11
	100	93
	100	92
	86	86
	100	87

SYNTHETIC APPLICATION

In order to demonstrate the usefulness of the new mediators in the Mitsunobu-type *C*-alkylation reactions, two insect pheromone analogs, **12** and **13** [8], and theonelladines C and D, **14** and **15** [9], were synthesized conveniently from **16** and **11**, respectively, in excellent overall yields [6,10].



Thus, through a series of investigations carried out in our laboratory, a number of mediators applicable to the Mitsunobu reaction have been discovered. These mediators should make the reaction more versatile, more colorful and more useful to the synthetic organic chemistry.

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